CLINICAL EVALUATION OF MIGRAINE AND OTHER SEIZURE RELATED HEADACHE IN PATIENTS WITH EPILEPSY

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BONAFIDE CERTIFICATE

This is to certify that the dissertation entitled **"CLINICAL EVALUATION OF MIGRAINE AND OTHER SEIZURE RELATED HEADACHE IN PATIENTS WITH EPILEPSY"** submitted by **Dr.C.SURESH KHANNA**to the Tamil Nadu Dr.M.G.R.Medical University, Chennai in partial fulfilment of the requirement for the award of D.M Degree, Branch I (Neurology) is a bonafide research work, was carried out by him under my direct supervision and guidance.

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DECLARATION

I, **Dr.C.SURESH KHANNA**declare that, I carried out this work on, "**CLINICAL EVALUATION OF MIGRAINE AND OTHE RSEIZURE RELATED HEADACHE IN PATIENTSWITH EPILEPSY**"at the Department of Neurology, Govt. Rajaji Hospital during the period of March 2012 to February 2013. I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any other University, Board either in India or abroad.

This is submitted to The TamilnaduDr.M.G.R.Medical University, Chennai in partial fulfilment of the rules and regulations for the D.M degree examination in Neurology.

Place : Madurai **Dr.C.SURESH KHANNA**

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INTRODUCTION

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Epilepsy and Migraine are the chronic disorders with recurrent neurological dysfunction associated with headache and autonomic,abdominal and psychotic features. In some patients it may be difficult to differentiate between migraine and the seizure episodes. Both are having comorbid symptoms and occurrence.Migraine patients can develop seizure and epileptics can have migraine attacks. Epileptologists proposed the hyperexcitabilty of the altered brain tissue, as the cause of seizure and migraine headache occurrence and vice versa.Enhancedhyperexcitability of cortical neurons and diminished threshold are the pathophysiological mechanisms enumerated in these conditions. Low magnesium in brain and the altered neurotransmitters are responsible for increased cortical excitability.Both the environmental as well as the genetic factors might cause these changes.

AIMS AND OBJECTIVES

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1.To study the incidence of various headaches which can occur periictally and interictally in patients with known primary generalised epilepsy.

2.To evaluate the association of headache, with the seizure and its impact on the patient's lifestyle.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Epilepsy and Migraine are the chronic disorders with recurrent neurological dysfunction associated with headache and autonomic,abdominal and psychotic features[1].In some patients it may be difficult to differentiate between migraine and the common epileptic attacks.In the developed countries epilepsy incidence in young persons are 100-200/1lakh/yr and >200/1lakh/yr in older population[2].The prevalence studies showed, total rate of 5-6/1000.The prevalence rate is somewhat constant in developed nations of variable geographical distributions.But highest, migraine prevalence is seen in American and European countries and lowest in asiancountries. Both epilepsy and migraine are inversely related with economic condition of people. A lifetime prevalence study revealed that as many as 93 per cent of men, experienced a headache at some time and the most common cause being the tension-type headache (69 per cent)[3]. For women, the lifetime prevalence was 99 percent.Here also tension-type headache is the most common (88 per cent)type. Although such a high prevalence suggests a commonplace, almost trivial symptom, it can nevertheless be a symptom of grave significance. It is thus a major cause for attendance in neurological outpatient clinics, representing approximately 15 per cent of routine neurological attendance and makes more anxious in both patients as well as doctor side. Thus every patient with headache must be given importance and needs complete investigations sometimes. Although most patients

with headache will not contact their doctor and those with frequent headache, and with migraine constitute a significant public health and economic problem.

In 1985, the International Headache Society (IHS) established a classification committee which published the first international headache classification in 1988, including the operational diagnostic criteria[4].This has been adopted by the World Federation of Neurology and the World Health Organization, which has incorporated the main features in the international classification of diseases (ICD-10). The classification provides 13 broad categories which are then subdivided, to allow for coding up to a four-digit level. The extent of the subclassification thus depends upon the degree of sophistication required. The classification has been an important advance, primarily for research but increasingly for clinical management. It is gradually replacing the previous variable terminology which included the classic migraine, common migraine, psychogenic headache, and essential headache.

Table 3.1. Classification of headache (data from Headache Classification Committee of the International Headache Society 1988)[13]

Migraine
Tension-type headache
Cluster headache and chronic paroxysmal hemicrania
Headache associated with head trauma
Headache associated with vascular disorders
Headache associated with non-vascular intracranial disorders
Headache associated with substances and their withdrawal
Headache associated with non-cephalic infection
Headache associated with metabolic abnormality
Headache or facial pain associated with disorders of cranium, neck, eyes, ears, nose sinuses, teeth, mouth, or other facial or cranial structures
Cranial neuralgias, nerve trunk pain, and differentiation pain
Other types of headache or facial pain
Headache not classifiable

Revisions of the IHS classification have been proposed. For example, refocusing on the old problem of patients with very frequent headache, often referred to as chronic daily headache or addition of new entities, such as the short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome have been proposed.

ANATOMY AND PHYSIOLOGY OF HEADACHE:

All the tissues which covers the cranium are pain sensitive mainly the arteries and the muscles, pericranium. The skull bone is insensitive to pain. Within the cranium, the venous sinuses and their tributaries, the dura mater and the cerebral arteries, and the fifth, ninth, and tenth cranial nerves are the chief pain-sensitive structures. The main factors causing headache have been considered to be:

- inflammation involving pain-sensitive structures of the head;
- referred pain;
- meningeal irritation;
- traction on or dilatation of blood vessels;
- pressure upon or distortion of pain-sensitive structures caused by tumours or other lesions; and
- psychological causes, when the pain is considered in some instances to be due to tension in the muscles of the scalp and neck.

However, such a classical view of headache production does not readily explain the mechanisms of headache in migraine and tension-type headache. A more precise understanding is now emerging which implicates, all levels of the innervation of cranial structures .The somatosensory innervation to the head is primarily from the trigeminal nerve and upper cervical spinal-cord segments[5]. The original studies by Penfield and colleagues on awake patients during the surgery identified that traction of the pain-sensitive meninges[6] and meningeal vessels[7] could give rise to severe headache, but by contrast, the brain parenchyma was not pain sensitive. The trigeminal innervation of the meninges and meningovascular structures are via the small, unmyelinated C fibres.Activation of the caudal trigeminal nucleus and the dorsal horn at the C1/2 level can be demonstrated by c-fos immunocytochemistry, a method for showing activation of cells following stimulation of both vessels and meninges in animals.Activation of trigeminovascular fibres is also accompanied by release of the neuropeptides, substance P, and calcitonin-gene-related peptide (CGRP)[8]. The second-order pathway from the caudal trigeminal nucleus is via the quintothalamic tract primarily to the ventroposteromedial nucleus of the thalamus .

Sensitization of the trigeminal pathway may be important in the generation of some headaches, for example that associated with migraine which can be exacerbated by coughing and sudden head movement. Exacerbation by movement is a classic feature of the headache associated with intracranial pathology, when it is thought to be due to the mechanical stimulation of meningeal vessels. In animals, recording of primary afferent neurons in the trigeminal ganglion has shown that chemical stimulation of the dural receptive field with inflammatory mediators[9] directly excites the neurons, but in addition, enhances their mechanical sensitivity. Thus neurons may be strongly activated by mechanical stimuli that normally excite little or no response .In addition to mapping the early components of pain processing, cognitive factors are increasingly recognized as being important in the central modulation of headache pain.

DIFFERENTIAL DIAGNOSIS AND CLINICAL APPROACH:

While asking headache details, following points must be paid more attention. How long does thepatient have headache? Is it increasing in severity? Is it constant or paroxysmal innature and if paroxysmal, what is the duration of the attack and do they occur at any special time of a day? Are the headaches precipitated by any circumstance or activity, and how can they be relieved? What is the character of headache and the situation? Is there associated tenderness over the scalp or skull, or visual disturbances, vomiting or vertigo? Had there been a head injury? Are

there symptoms of nasal obstruction or discharge, either from the nose or into the pharynx? Is the patient anxious, tense, or depressed? Physical examination should include a general assessment which must include the blood pressure.

Investigations will be dictated by the history and the findings; ranging from the ESR and temporal artery biopsy in patients whose history is indicative of cranial arteritis, through to neuroimaging. The decision of when to undertake neuroimaging can be difficult. Many features may influence the decision, including the anxiety of the patient and referring physician. However, patients with long-standing symptoms of tension-type headache are rarely found to have an underlying structural lesion. Similarly, patients with a typical history of migraine need not undergo neuroimaging. Thus, in a previous study of 547 patients with a typical history and normal examinations, only four had an abnormality on CT scan.

TENSION HEADACHE AND DEPRESSION:[3]

Headache is one of the most common phenomenon, experienced by most persons in their life , particularly during stress and fatigue.

One of the most commonpresentations of headache is a sense of pressure over the vertex or the sense of a tight band that is present most of the day, but is usually worse in the evening. It is quite often felt in association with anxiety and in some patients with depression, although it may be difficult to know which was the causeandtheeffect. The IHS classification uses the term ‘tension-type headache’, to

imply in some patients, an abnormality of pericranial muscle. It is classified either as episodic or chronic type. It is likely that the underlying pathophysiology is heterogenous. Although there may be sensitive trigger points in pericranial muscles, it has been difficult to demonstrate abnormalities consistently with electromyogram (EMG) studies. Patients with other headaches, such as migraine, often suffer from coexistent tension-type headache. The headache does not usually interfere with daily activity and is less often exacerbated by physical activity than migraine. Similarly, photophobia, phonophobia, and nausea are much less prominent than with migraine and typically the headache is bilateral rather than unilateral in nature.

Tension headache can be difficult to treat. Simple analgesics may provide relief, and ibuprofen is generally the first choice before aspirin. The use of a tricyclic antidepressant as a prophylactic, starting at a low dose (for example 10–25 mg of amitriptyline), can be beneficial .A danger in the treatment of tension-type headache, however, is a vicious cycle of increasing medication, with the emergence of drug-induced headache which can change the pattern of episodic tension type headache into a chronic one. Drug-induced headache is most commonly recognized in the headache clinics, where patients present with a long history of migraine or, less commonly, tension-type headache .The withdrawal of analgesics in regular users can result in a rebound headache, thus leading to

sustained high levels of analgesic consumption. Withdrawal of caffeine, which is used in a number of migraine medications, can also result in rebound headache .A careful analgesic drug history is important. Although withdrawal of analgesics and/or caffeine may initially exacerbate symptoms, it can often change chronic tension headache into a more manageable episodic pattern.Patients with depressive illness often have coexistent headache, which can be delusional in nature. Sometimes these patients will have night-time headache or early morning headache due to the disturbed sleep pattern with early morning awakening.

MIGRAINE:

Migraine headache is known to medical science for nearly 2000 years[11]. In the first century of the Christian era, Aretaeus of Cappadocia referred to it as heterocrania, and the term hemicrania (migraine derived from this word) was introduced by Galen (AD 131–201). A key feature of migraine headache is that it is periodic in nature , with attacks lasting usually between 4 and 72 hours[12]. Typical features, although not exclusive, are that it is usually unilateral and pulsatile in nature. Operational diagnostic criteria (International Headache Classification) require that the headache is associated with nausea or vomiting and/or photophobia or phonophobia. The headache itself may or may not be associated with an aura of preceding neurological symptoms. During the latter, characteristic changes in brain blood flow may be demonstrated.

FREQUENT MIGRAINE:

Recurrent attacks of headache lasting for 4-72 hrs with the following features and with normal physical examination and no secondary causes for headache.

Atleast two of[32]

1.Unilateral headache

2.Throbbing type

3.Movement aggravation

4.Moderate to severe in nature

Atleast 1of the following

1.Nausea or vomiting

2.Photophobia ,phonophobia

The International Headache Classification (Headache Classification Committee of the International Headache Society 1988)[13] distinguishes between migraine with aura and migraine without aura .The former subsumes a number of migraine subtypes or variants. This classification replaces the earlier terms of classic migraine, referring to those with aura, and common or simple migraine, referring to those without aura. The new classification is quite explicit and avoids confusion.

Migraine with and without aura can, of course, both occur in an individual patient. Migraine with aura is most common in women around 12-13yrs(14.1/1000 person /yr) but without aura peaks in between 14-17yrs(18.9/1000 person yrs)[14]of age.Migraine with aura occurs early in boys(6.6/1000/yr at five yrs) and consequently more prevalent in boys than in girls.Menstrual hormones are responsible for the increased risk of migrainous headache at menarche and also during the reproductive life period of the women.

Both Migraine and seizure disorder have comorbid symptoms and occurrence.Migraine patients can develop seizure and epileptic patients can have migraine attacks.Migraine prevalence is 24% between the epileptic probands and 26% in their relatives.1-17% is the epilepsy prevalence in migraineurs[15]. To explain the comorbidity there are 3 models available now. Unidirectional causal link is the first possibility. If migraine produces seizure by causing cerebral ischemia, then the migraine incidence will be more before seizure occurs.Conversly by the induction of trigeminovascular[15] system, epilepsy can cause migraine, in whichcase migraine incidence will be more after epileptic attack.So the unidirectional link was rejected, because of the increased risk of migraine prior to and after the seizure. Environmental factors will share the next possibility .Since migraine is more common in elderly individuals having

cryptogenic seizure, the unidirectional link was also deleted.Third possibility, deals with the genetic susceptibility between these 2 conditions.

Finally epileptologists proposed the hyperexcitabilty of the altered brain tissue,whichcan raise the risk of seizure and migraine headache ,and vice versa, as the most suitable explanation.Enhancedhyperexcitability[16] of cortical neurons and diminished threshold are the pathophysiological mechanisms enumerated in these conditions. Low magnesium in brain and the altered neurotransmitters are responsible for increased cortical excitability.Both the environmental as well as genetic factors might cause these changes.

TEMPORAL RELATIONSHIP AMONG EPILEPSY AND MIGRAINE SYMPTOMS:[17]

In epileptic patients headache can occur during

a)Ictal

b)Pre&Postictal and

c) Interictal state.

Migraine without aura as well as tension type headache are more common in preictal and in periictal periods. Spreading depression,neurotransmitter alterations are the causes of higher incidence of migraine headaches during epileptic attack[18].

Patients usually will not tell the preictal and ictal headaches because of the seizure but if we carefully ask they will tell the headache.Ictal headache can be an isolated manifestation of a seizure or a predominant symptom of a seizure.It usually occurs in the frontal region as a throbbing type of headache lasting for <1mt of mild to moderate severity.Hemicranial pain can occur with parietal lobe epilepsy. Postictal headache is the most common type of headache in Occipital lobe epilepsy and in Mesial temporal sclerosis,the post ictal headache occurs very frequently .Unilateral and frontotemporal region is the commonest site of headache .Tension headache can occur in postictal period.Headache can be provoked by seizure. Likewise seizure can be initited by migraine aura which is called as Migralepsy. IHS-ii criteria(2004) for migralepsy require[19]:

1.Migraine headache fulfilling the criteria to say migraine with aura.

2.Seizure that occurs within 1hour of migraine with aura.

Migraine triggered seizures commonly associated with basilar migraine and catamenialepilepsy.In sometimes, Basilar migraine can be difficult to differentiate from complex partial seizures.Catamenial epilepsy and migraine with aura, are interchangeable risk factors for migralepsy.

EPILEPTIC SYNDROMES,MIGRAINE AND MIGRAINE LIKE SEIZURES:

In idiopathic childhood occipital lobe epilepsy and Rolandic epilepsy migraine and migraine like seizure can occur.In most patients with occipital lobe epilepsy, family history will be present and 25-40% of them will have headaches following seizure.Headache most commonly occur during the onset of seizure can be misdiagnosed as migraine.Rolandicepileptics can develop headache, during seizure evolution and many of them develop migraine after the seizure.

EPILEPSY AND FAMILIAL HEMIPLEGIC MIGRAINE GENETICS:

FHM is an autosomal dominant disorder and it is a variant of migraine with aura.In type 2FHM there may be a loss of sodium potassium ATPase function which may depolarize the cortical neurons producing hyperexcitability and then fits.In, FHM3 mutation in the SCN1A gene can cause GEFS plus and myoclonic epilepsy.Fits can occur during the hemiplegic migraine attack.It may be partial or generalised or secondarily generalised and it may occur initially or during the episode of headache.Ion channel dysfunction is the key for both neuronal hyperexcitability and cortical spreading depression[20].

Migraine can produce cortical infarcts which can initiate seizures.Thus patients with epilepsy having migraine also, will have a poor prognosis. Migraine may be associated with increased risk of ischemic stroke in women but not in

men.Channelopathies[21] are the basis for genetic linkage between these two interrelated disorders.Focalcerebaledema in the suparatentorial region can occur with migraine triggered fits.EEG is usually normal, though diffuse slowing can occur.IHS classification highlights 3 conditions like migraine-triggered seizure,hemicraniaepileptica and post ictal headache.

HEMICRANIA EPILEPTICA:

Criteria include:

1)Headache lasts for seconds to minutes, with migraine features fulfilling criteria 3,4.

2)Partial seizure

3)Headache develops simultaneously and to the same side of ictal activity.

4)Complete resolution of headache after fits.

Its very difficult to differentiate between the post ictal headache and the migraine headache which is associated with nausea,vomiting.

Post –ictal headache criteria for diagnosis:

1)Tension type of headache or migraine type in migraine patients fulfilling criteria 3,4.

2)Partial or generalised seizures

3)Headache occurring within 3hrs of seizure.

4)Resolution oh headache within 72hrs of seizure.

Epilepsy and Migraine are chronic disorders with several episodes of neuronal dysfunction[21].Both will come to baseline in between.Several triggering factors like visual ,menstruation,sleepinadequacy,intercurrent illness will be shared by both of theseconditions.Because of the hyperexcitability of cortical neurons sodium valproate like anticonvulsant drugs are used in the migraine prophylaxsis.In idiopathic childhood occipital lobe epilepsy and Rolandic epilepsy, migraine and migraine like headache can occur.In most patients with occipital lobe epilepsy, family history will be positive.25-40% of them will have headaches following fits.Headache that occurs during the onset of seizure can be often misdiagnosed as migraine.Rolandic epileptics can develop headache during the seizure evolution and many of them develop migraine after seizure.

Table 3.2. Classification of migraine (data from Headache Classification Committee of the International Headache Society 1988)[22]

Migraine without aura

Migraine with aura

- Migraine with typical aura
- Migraine with prolonged aura
- Familial hemiplegic migraine
- Basilar migraine
- Migraine aura without headache
- Migraine with acute-onset aura

Ophthalmoplegic migraine

Retinal migraine

Childhood periodic syndromes that may be precursors to or be associated with migraine

- Benign paroxysmal vertigo of childhood
- Alternating hemiplegia of childhood

Complications of migraine

- Status migrainosus
- Migrainous infarction

Unclassifiable migraine-like disorder

Migraine is an extremely common condition. Recent epidemiological studies, using the IHS criteria, suggest a prevalence in women, between 15 - 20% and in men between 5 - 10% and in some studies even higher in women. There is a strong family history, reported in migraine sufferers, particularly in those suffering from migraine with aura.

PATHOPHYSIOLOGY:

The traditional view of the pathophysiology of migraine has been that of arterial spasm within the internal carotid territory resulting in the aura, followed by dilatation in the distribution of the external carotid artery, resulting in the headache. The original evidence in support of this, included the observation that amyl nitrite could temporarily abolish the visual scotoma[23] and that cerebral infarction or occlusion of retinal arteries could both occur during the aura phase, showed that the headache is due to arterial dilatation, mainly of the extracerebral arteries of the dura and scalp, and other branches of the external carotid, with the clinical concomitants of congestion of the conjunctiva and nasal mucosa in some patients and pulsation of the superficial temporal artery on the same side where the headache is experienced.

The specific therapeutic effect of ergotamine is thus interpreted as being due to the constriction of the branches of the external carotid artery. This simple interpretation, particularly with respect to vasoconstriction, has been challenged following the seminal observations of focal hyperaemia followed by a slow spread of reduced blood flow which outlasts the aura. This slow spread of oligemia which transcends specific arterial territories has been compared to the spreading depression of Leao[23].

Neuronal depolarization is followed by suppression of neuronal activity, which spreads at a rate of approximately 3–4mm/min, independently of the vascular territory. This is similar to the rate of spread of reduced blood flow and the calculated rate of spread of neuronal dysfunction in the occipital cortex to account for the slow progression of the visual scotomata.

The opportunistic study of a patient undergoing a positron emission tomography study who developed a migraine, has confirmed bilateral hypoperfusion starting in the occipital lobes and spreading anteriorly at a constant rate, independent of cerebral artery territory. The maximal decreases in flow were in the order of 40 per cent.Similar studies with functional magnetic resonance imaging demonstrate significant reductions in perfusion during the aura phase.Additional evidence relating these changes directly to alterations in neuronal excitability have been provided by magnetoencephalography with suppression of neuronal signal during

the migraine aura.These imaging studies during migraine headache with aura, increasingly support the view that, perfusion changes are secondary to a primary neuronal dysfunction[24].

A number of biochemical correlates of the migraine attack have been observed. Serotonin (5-hydroxytryptamine; 5-HT)[25] constricts large arteries and dilates arterioles and capillaries, and there is a widespread subcortico-cortical projection system from the midbrain raphe nucleus which utilizes serotonin as its neurotransmitter.

The urinary excretion of the serotonin metabolite 5-hydroxyindolacetic acid is increased in severe attacks, indicatingtherelease of serotonin into the circulation.Injection of reserpine, which causes release of serotonin, can also precipitate attacks in vulnerable subjects. Platelets release serotonin, and platelet aggregation is abnormal in migraineurs. Platelets have also been demonstrated to have decreased monoamine oxidase activity.

These observations of platelet abnormality and the fact ,that they release serotonin has given rise to the theory that peripheral platelet function is a principal factor in the pathogenesis of migrain.It now seems unlikely that an impairment of peripheral function is directly responsible ,although it might reflect a more general abnormality of serotonin function. Alternatively, these peripheral events may be neurally mediated since trigeminal stimulation leads to platelet aggregation and

mast-cell degranulation.Importantly, sumatriptan and other newer drugs of the same class are potent 5-HT_1 agonists. Recent cloning of the 5-HT receptor subtypes has resulted in more precise classification and, specifically, sumatriptan and its analogues are 5-HT_{1B} (vascular) and 5-HT_{1D} (presynaptic neuronal) agonists.

There is no generally accepted theory that encompasses all of the observed vascular changes and the central and biochemical correlates of migraine.Trigeminovascular system(neurogenic inflammation)[26] and a variety of vasoactive peptides, including calcitonin-gene-related peptide, are involved inheadache initiation. The release of peptides and the plasma extravasation can be blocked by sumatriptan.

Stimulation of the superior sagittal sinus or meningeal irritation also causes activation of the caudal trigeminal nucleus and its extension into the upper cervical cord. This can be demonstrated by c-fos immunocytochemistry which indirectly demonstrates cellular activation. Activation can also be blocked by antimigraine drugs such as dihydroergotamine.Since the sinus and trigeminal nerve supply are stimulated directly, the pharmacological antagonism must be central. Importantly, neocortical spreading depression will also provoke c-fosimmunoreactivity within the trigeminal nucleus.Recently, a PET study during an acute migraine headache attack demonstrated an increase in cerebral blood flow within medial brainstem

structures which persisted for a time, after symptom relief withsumatriptan. The precise location of the increased blood flow was beyond the resolution of the imaging system, but might have related to the locus coeruleus and dorsal raphe nuclei .

No adequate theory ,yet exists to encompass all of these observations and, no doubt, many further molecular candidates will be proposed. The discovery of the importance of nitric oxide as a transmitter, both centrally and peripherally, has also directed attention to a possible role in migraine .

Finally, important advances can be anticipated, arising from the impact of molecular genetics on our understanding of migraine. A major clue has come from studies of families with cerebral autosomal dominant arteriopathy with subcortical infarcts and leucoencephalopathy (CADASIL)[27].

Following demonstration of linkage to chromosome 19 in CADASIL families, similar linkage was observed in patients with familial hemiplegic migraine. The gene for CADASIL has recently been cloned, and shown to be the Notch 3 gene ,a gene with some functional similarities to the presenilins.The potential relationship of mutations in this gene to those families with coincidental migraine is unclear. By contrast, the linkage to chromosome 19 in families with hemiplegic migraine[28] has been established as being due to mutations in a brain-specific P/Q-type calcium channel α1-subunit gene, CACNL1A4.The role of this channel in migraine

pathophysiology is not yet clear, but progress can be anticipated from transgenic mouse models.

CLINICAL FEATURES:

The age of onset is often at, or shortly after, puberty and less frequently in middle or later life, although in women onset around the menopause does occur, sometimes without the accompanying headache, which can lead to diagnostic difficulties. Migraine is less common prior to puberty, but cyclical vomiting and motion sickness are common in children who subsequently develop migraine. The frequency of attacks varies largely. Sometimes they occur 2-3 times a week, whereas few may have only one or two eoisodes in their lifetime. 1-2 attacks per month is a common one. Headache may be more frequent at the time of menstruation and commonly decrease in frequency at the time of pregnancy. The common pattern is towards reduction in frequency with age, and sometimes the headache completely disappears leaving only an aura .

It is often said that migraine sufferers have a perfectionist or obsessional character, but in a disease that is so common, this is difficult to establish. Certainly migraine can occur after a period of excitement or excessive work. Sometimes this is due to extra sleep at a time of relaxation, so-called weekend migraine. Minor trauma can also precipitate migraine ,such as bright lights and, in some patients, strong smells, like wet paint. Dietary precipitants are often sought, but rarely found. Those

thought to be responsible include, dairy products, particularly cheese, chocolate, fruit, and most commonly caffeine and alcohol. Missing meals may also precipitate an attack.

Headache is the most characteristic symptom of migraine and the one from which it derives its name. It may be the only manifestation, where it is referred to as migraine without aura (common migraine); indeed this is probably four times as common as migraine with aura (classical migraine). The headache may be preceded by premonitory symptoms,the most common of which are lassitude, hunger, and slight looseness of the bowels. On occasions the patient may feel exceptionally well and energetic before an attack. The onset may occur during the day, but can awake the patient in the morning, particularly from a heavy, deep sleep.Rarely, the attack may awaken the patient during the night. Typically the pain is localized to one side, often in the temple, and starts as a boring pain, which then gradually spreads until the whole side of the head is affected. As it increases in intensity it tends to acquire a throbbing character, which is intensified by stooping and by all forms of exertion. Although usually unilateral, a significant number of cases become bilateral and often, late in an attack, the pain moves posteriorly to an occipital distribution. The headache builds up to a maximum over about 30 min and lasts from hours to 1 or 2 days. It is usually relieved by sleep, although patients may be left feeling fatigued and with a mild headache while

getting up in the next day. In the majority of cases nausea occurs, but only in about 50 per cent of the patients, vomiting occurs. There is an occasional diarrhoea. Photophobia and phonophobia occur during the attacks and patients usually prefer to lie quietly in the dark, in contrast to cluster headache, when the patient will move around.

Vasomotor changes are often conspicuous. The face is often pale and the extremities cold, until improvement begins, but congestion of the face, conjunctiva, and nasal mucosa may occur, often confined to the side of the headaches. There may even be subconjunctival haemorrhage or bruising around the eyes. The superficial temporal artery on the affected side is often seen to be congested and pulsating vigorously, and some patients can obtain temporary relief by pressing over the temporal artery or the carotid, although release of compression often results in worsening of the headache after a minute or so. There is quite often polyuria following recovery from the attack.

When the headache is accompanied by an aura (migraine with aura)[29] the aura usually precedes, but may accompany, the headache. The headache is indistinguishable from that which occurs with migraine without aura, although it may be more commonly unilateral. Patients often have a combination of headache attacks, both with and without auras.

Visual disturbances are the commonest auras[30]. These are usually homonymous, involving the corresponding halves of both visual fields, although patients often experience them as being worse in one eye than the other.The visual disturbance is commonly characterized by positive phenomena at the outset, with a bright spot appearing near the centre, or in the periphery, which gradually expands and the advancing edge exhibiting scintillating figures (teichopsia)[31] which may be coloured and angular. The zigzag patterns are characteristic and referred to as fortification spectra. The spreading scintillation, leaves behind it an area of blindness, so that when it reaches the periphery or the centre of the half-fields the patient is hemianopic, although this is more often difficult to demonstrate on examination. The progression of the visual disturbance lasts from 15 to 20 minutes and the hemianopia then gradually fades away. The whole disturbance lasting about half an hour, although objects in the affected fields may appear less bright than normal for several hours. The disturbance may have a homonymous quadrantic distribution, or much less commonly, all peripheral vision is lost in both fields, leaving only a 'telescopic' field of vision.Exceptionally, the hemianopia is bilateral, giving temporary blindness. Patients may also experience macropsia or micropsia.Auras of paraesthesiae and numbness occur next in frequency. These symptoms occur in a 'cortical' distribution, involving the periphery of the limbs and the circumoral region[32]. The upper limb is more often affected, paraesthesiae ,

beginning in the fingers and gradually spreading up the limb, taking 5–20 min to do so. The proximal part of the arm is often relatively spared. The lips, face, and tongue may be subsequently affected on one or both sides, or can be involved without the upper limbs. Frequently, patients give a history of only half of the tongue being affected. The lower limb is only rarely affected. Paraesthesiae usually develop shortly after the onset of the visual disturbances, but may occur without the latter as the first symptom, or after the headache has been present for several hours. Olfactory and auditory hallucinations have been reported, but are rare. Mild weakness of the limb, usually the upper, may develop following the paraesthesiae, and in rare instances transient hemiparesis occurs with each attack(Hemiplegic migraine)[33].Aphasia is usually of the expressive type and is accompanied by dysgraphia. In right-handed people, it is usually associated with visual disturbance in the right hemifield and paraesthesiae in the right hand and face. Patients often complain of difficulties with concentration, and may feel disorientated in space and time.

The characteristic feature of migraine attacks is the slow speed of the developing neurological disturbance. This has been attributed to spreading cortical depression, which travels over the cortex at a rate of about 3 mm/min ,by contrast to the rapid neural excitatory spread of focal seizures. Similarly, transient ischemic attacks , have a much more rapid progression. The characteristic history is of great

importance when one encounters patients who have the migrainous aura without headache[34]. Attacks often become less frequent with age, with lessening of the headache and vomiting, and patients may ultimately only experience the aura.

TREATMENT:

Management principles:

It is very important to explain the patient that

1)Since migraine is caused by his genes it could not be cured but can be controlled.

2) Drugs and lifestyle changes will influence headache severity.

3) Migraine will not cause death but can cause serious morbidity.

4)Migraine management needs patient co-operation.

NONDRUG THERAPY;

Regular diet,healthy lifestyle ,relaxation therapy and avoiding precipitating factors like coffee and chocolates, alcohol intake and avoidance of stressful life can alter the prognosis of migraine. Extensive changes in diet are usually unrewarding. Concomitant drugs should be reviewed, such as vasodilator drugs and the oral contraceptive pills.

PREVENTIVE MANAGEMENT:

The basis for preventive strategy is a combination of acute attack frequency and also the attacktractability.Severeheadches and headache lasted for more than 15 days per month for more than 3months require additional prophylaxis[40].Several drugs starting from beta blockers,tricyclics,Calcium channel antagonists,and anticonvulsants like sodium valproate are available to treat migraine recurrence.Minimum of 6 months, the prophylaxis drugs have to be continued for full clinical benefit.Always start in low dose then gradually titrate according to the response.Neuromodulation therapy in the form of occipital nerve stimulation is a promising one which modified the thalamic pain integration. This is an interesting and developing one.

Drug treatment can be divided into two categories, namely treatment of the attack and prophylaxis[34]. Many attacks can be controlled by aspirin, paracetamol, or other simple analgesics, in combination with an antiemetic drugs such as domperidone. The key is to take the drug early in the treatment. Narcotic analgesics should be avoided. The mainstay of symptomatic treatment has, in the past, been ergotamine or dihydroergotamine. This still has a role, although one has to be aware of the dangers of exceeding a weekly dose of 2–4 mg, the problems of frequent, even small doses, and the fact that ergotamine in itself can cause headache in overdose. Recently, the introduction of the 5-$HT_{1B/1D}$ agonist, sumatriptan, and similar drugs

such as naratriptan, rizatriptan, and zolmitriptan, are rapidly becoming first-line treatment for the acute attack.Sumatriptan is effective in migraine with or without aura, both as an oral and a subcutaneous preparation.Subcutaneous administration of 6 mg of sumatriptanimprovesnearly 90 per cent of migraine attacks .The headache, in responders, settles in 30 min or so, and only a few patients require further doses.

Migraine attacks in relation to the menstrual cycle can be treated prophylactically on a more circumscribed basis. Aspirin, twice daily, may be effective ,but the three mainline drugs are the 5-HT antagonist pizotifen, the β-adrenoreceptor antagonist propanolol, and sodium valproate. These all have a similar efficacy. However, each has side-effects, and propanolol is contraindicated in patients with asthma, and sodium valproate should be used with caution in women of childbearing age who may become pregnant.

Methysergide is highly effective, but in view of the side-effect of retroperitoneal fibrosis, is only reserved for treatment-resistant cases. Some patients, particularly those with more frequent attacks,will respond well to tricyclic antidepressants, often in low dosage, such as amitriptyline10-25 mg/day.Patients with status migrainosus are best admitted to hospital for fluid replacement, correction of electrolyte imbalance, and management of the nausea and vomiting. Some patients may benefit from treatment with steroids.

MIGRAINE VARIANTS:

1.OPHTHALMOPLEGIC MIGRAINE:

This term has been applied to recurrent attacks of headache, usually orbital or retro-orbital, associated with paralysis of one or more oculomotor nerves. Although transient diplopia may occur with migraine, the isolated oculomotor palsies of ophthalmoplegic migraine can rarely persist for days or weeks after the attack, and sometimes become permanent .The third nerve is most commonly involved, but rarely the fourth, and the first division of the fifth may be affected. The diagnosis should be accepted with care when used to account for ocular palsies lasting more than an hour or two, as many such cases hitherto described may have had intracranial aneurysms. However, in a review of the ophthalmological complications of migraine, theophthalmoplegia, either isolated or recurrent, occurring in migrainous attacks, often remained unexplained despite full investigation.

Ophthalmoplegic migraine appears to be extremely rare. Many structural lesions can give rise to a similar feature, and in particular, Tolosa–Hunt syndrome, which is responsive to steroids, can mimic ophthalmoplegicmigraine.The diagnosis should not be accepted without scrupulous investigation and neuroimaging.

2.HEMIPLEGIC MIGRAINE:

Transient hemiparesis can occur with migraine headache. Hemiplegic migraine can be sporadic or familial. The EEG during the attacks may show slow waves over the hemisphere contralateral to the hemiplegia, but neuroimaging is usually norma .Respiratory arrest during an attack, may lead to death.Occasionally a mild CSF pleocytosisoccurs.In sporadic hemiplegic migraine, the weakness can affect alternate sides. In the familial form, it is usually on the same side. A mutation in a brain-specific calcium channel α1-subunit gene has been linked to familial hemiplegic migraine .

3.BASILAR MIGRAINE:

In 1961, Bickerstaff described attacks of migraine, starting most commonly during adolescence, in which the symptoms of the aura suggested,ischaemia in the distribution of the posterior circulation .The attacks commonly begin with classical visual disturbances of migraine which are usually bilateral, followed by paraesthesiae of the lips, hands, and feet. Dysarthria and diplopia in association with severe occipital headache may then follow. Impairment of consciousness with stupor has been attributed to involvement of the brainstem reticular formation .

4.RETINAL MIGRAINE:

Unilateral photopsia, monocular altitudinal defects, and transient monocular blindness indicate involvement of the retinal circulation and, when occurring in isolation with migraine headache, suggest a diagnosis of retinal migraine. Thrombosis of the central retinal artery and of single branches may occur and recurrent attack of retinal ischaemia may lead to bilateral optic atrophy due to ischaemic papillopathy.Some patients with retinal migraine have aortic valve abnormalities on echocardiography.

5.LOWER HALF MIGRAINE:

Some patients experience episodic pain which is predominantly in the nose, ear, and neck, referred to as lower-half headache or facial migraine. Recurrent attacks of cervical pain with tenderness over the carotid (carotidynia) may occur in association with migrainous headaches, and in such cases the symptoms usually respond to antimigrainepreparations .

COMPLICATIONS OF MIGRAINE:

Rarely patients can have very frequent attacks of headache, and finally the migraine, with a persistent aura, may last many days with little to no relief (status migrainosus).Most commonly dehydration and fatigue are the contributing factors.Sometimes, a persistent hemiparesis can occur in hemiplegic migraine.Likewise , a hemianopia may persist & sometimes associated with

prolonged positive visual phenomena. In these situations CT evidence of ischaemic infarction may be seen.Some patients with the antiphospholipid antibody syndrome ,develop increasing attacks of migraine and are at risk of migraine-associated cerebral infarction. The presence of antiphospholipid antibodies is an independent risk factor for cerebral infarction and such patients with a combination of migraine and antibodies should be anticoagulated. It is often assumed that in patients with a permanent visual field defect, hemiparesis, aphasia, or ophthalmoplegia, an intracranial vascular anomaly (e.g. aneurysm or angioma) will be present, but a review of cases of 'complicated migraine' showed that investigations designed to demonstrate such lesions are usually negative .An association between the migraine and seizure has been found in some clinical studies and occasionally a seizure event can occur at the height of a severe migraine attack.

CLUSTER HEADACHE:

MIGRAINOUS NEURALGIA:

The term cluster headache was introduced by Kunklereferring to the characteristic pattern of attacks occurring in clusters. This has superseded the earlier term of 'periodic migrainous neuralgia' applied by Harris.Syndromes referred to by earlier neurologists as ciliary neuralgia, vidian neuralgia, and sphenopalatine neuralgia are

almost certainly the same condition ,the terminology reflecting various theories of pathogenesis in vogue at the time.

The headache is highly distinctive and involves chiefly the eye and frontal region on one side and is characterized by its periodicity. Attacks may occur once or several times in 24 hours and last from 10 minutes to, rarely, several hours. The pain is intense, even leading to attempted suicide; it is continuous and of ‘boring’ or ‘burning’ character. Typically the attacks may awaken the patient from sleep in the early morning, coincident with the first REM (rapid eye movement) state. During the attack, the patient paces up and down, in contrast to the behaviour in migraine attacks.

An attack tends to last for several weeks, after which the patient is free from symptoms for months or even 1–2 years before the headache recurs. Lacrimation and nasal congestion on the affected side, occur during the attack. Some patients have a sense of facial and palatal swelling ipsilaterally, which can occasionally be observed.There are no abnormal physical signs, although a Horner's syndrome, either transient or permanent, sometimes develops on the affected side and has been attributed to damage to the sympathetic fibres in the wall of the carotid artery.

Cluster headache is most common in males and usually begins in the third or fourth decade.It is far less common than migraine. In headache clinics, the ratio of migraine to cluster headache patients has been reported to be as high as 10 :

50.However, patients with cluster headache are far more likely to be referred to a specialist clinic and this overestimates the prevalence. Population-based studies in the USA suggest a prevalence for men of 0.4 per cent and for women of 0.08 per cent . Overall prevalence is unlikely to be more than 0.1 per cent. The fact that it can be precipitated by vasodilator drugs such as nitroglycerine and histamine or by alcohol, and that acute attacks are relieved by oxygen, has suggested that vasodilation might be involved. However, this is difficult to demonstrate.

The autonomic features are due to parasympatheticactivation.During an attack, an increase in neuropeptides, namely calcitonin gene related peptide (CGRP) and vasoactive intestinal polypeptide (VIP), the latter a marker for parasympathetic activity, have been found in ipsilateral jugular blood.

In view of the clustering, prophylactic therapy is the mainstay of treatment for those with very regular attacks. Education and explanation is important, including the avoidance of triggering factors, such as alcohol, during a cluster. Altitude may also precipitate attacks. Verapamil (80 mg four times a day) is an effective prophylactic, followed by lithium with appropriate monitoring of levels. Combination with a late-night ergotamine preparation, either orally or as a suppository, may help those patients whose attacks are typically triggered during early sleep.Prednisolone (40 mg daily in a reducing dose over 3 weeks) can be

valuable but should only be given in a short course.Other drugs that may have benefit include propranolol, methysergide, and pizotifen[36].

For acute attacks, ergotamine preparations are efficacious, and subcutaneous sumatriptan (6 mg) is effective in the majority of patients ,Oxygen inhalation in effective but the equipment can be cumbersome[37].The typical history provides the diagnosis and extensive investigation is not required. The non-specialist may misinterpret the history as being trigeminal neuralgia, and in some instances, an overlap syndrome can occur, the so-called 'cluster–tick syndrome', often related to vascular compression .Glaucoma should rarely cause confusion but is an important diagnosis, not to miss. Occasionally, cluster headache can be symptomatic of lesions in the cavernous sinus, and atypical histories or those occurring for the first time in the young or old should prompt investigation.

In some patients, the periodicity does not occur.The Headache Classification Committee criteria for chronic cluster headache is that, the attacks of pain occur for more than a year on a daily basis without a remission lasting longer than 2 weeks. This chronic cluster headache may develop de novo or follows, episodic cluster headache with increasing periods of attack and reducing remission time. Patients with chronic cluster headache often require lithium.

PAROXYSMAL HEMICRANIA:

Paroxysmal hemicrania shares, with cluster headache the unilateral severe ocular or periorbital and frontal pain , with associated autonomic disturbances of lacrimation, rhinorrhoea, and conjunctival injection. The attacks are very frequent, ranging from 2 to as many as 40 times a day, and tend to be shorter than those of cluster headache, ranging from a couple of minutes to half an hour .The key feature of chronic paroxysmal hemicrania is the response to indometacin in a dose of 150 mg a day or less. This is an absolute criterion for the diagnosis.

More recently, episodic paroxysmal hemicrania has been described with a periodicity similar to that of cluster headache, but otherwise the same features as chronic paroxysmal hemicrania. Hemicrania continua can also be episodic or chronic and is characterized by a constant hemicranial headache with exacerbations that can be associated with ipsilateral autonomic features. The sine qua non of the diagnosis of the hemicranias is the absolute responsiveness to indomethacin.

Short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome is characterized by very brief attacks of unilateral headache with autonomic phenomena[38]. The attacks last only from 30 seconds to 2 minutes and may occur many times in an hour. These paroxysmal headaches are all very rare.

There are several causes for secondary headache .Ophthalmological,dental and Otological problems can produce headache.Several intra and extracranial lesions and systemic problems were also included as the cause for headache.

ALTERATIONS OF NEURONAL EXCITABILITY IN EPILEPSY:

A number of factors can control neuronal excitability.These include voltage-gated ionchannels, neurotransmitter ligand activated ion channels,neuromodulators and second messenger systems[15].Ligand gated ion channels are responsible for communication between the cells while voltage gated channels determine, how inhibitory and excitatory influences are integrated in a way that determines the propagation of impulses to other neurons[37].

VOLTAGE GATED CHANNELS:

Voltage gated ion channels are membrane-spanning proteins composed of different subunits that when open permit the passage of ions.Most channels will open on depolarization of the membrane but some open when the membrane is hyperpolarized.Voltage gated sodium channels are intimately involved in the propagation of action potentials,the rapid upstroke being due to an opening of fast transient channels at about -60Mv.The importance of voltage gated sodium channels in human epilepsy is further emphasised by the finding of molecular

abnormalities in families with generalised epilepsy and febrile seizures and in patients with severe myoclonic epilepsy of infancy.

Voltage dependent calcium channels contribute to dendritic spikes,slow somatic depolarizations and associated burst discharges and by doing so trigger neurotransmitter release.Six subclasses of calcium channels are known to exist.L,N,T,P,Q and R,T channels have a low threshold of activation at around -70mV.They inactivate relatively rapidly.These channels are found, in high concentrations in thalamic neurons and play an important role in generation of generalised spike wave discharges. A mutation of CACNA1A has been found in a patient with absence epilepsy[34].

Voltage gated potassium channels are very diverse in their nature.They appear to play an important role in the regulation of repetitive firing by prolonging the after-spike hyperpolarization and slowing down the firing rate.Mutations of KCNQ2 and KCNQ3 encoding K+ channels subunits can lead to benign neonatal convulsions.The potentiation of voltage dependent potassium currents being explored as a potential target for new antiepileptic drugs.

INHIBITORY NEUROTRANSMISSION:

GABA is the major inhibitory neurotransmitter in the forebrain,being present at approximately 30% of all synapses in the central nervous system.Binding of

GABA leads to an opening of the chloride and potassium ion channels and resultant hyperpolarization.[16]The activity of benzodiazepines and barbiturates at GABAa receptor appears to be responsible for their antiepileptic activity.Mutations of GABRG2 gene encoding for GABAa subunits have been found in generalised epilepsy and febrile seizures[34].

EXCITATORY NEUROTRANSMISSION:

The major excitatory neurotransmitters are the amino acids L-glutamate and L-aspartate.They exert their synaptic influences by interacting with a number of different types of receptors.AMPA[33] receptor is probably responsible for the majority of the rapid excitatory neurotransmission.Thekainate receptor is also coupled to a channel permeable to sodium and potassium.Opening of channel allows the entry of both sodium and calcium.This acts as an amplification mechanism that leads to prolonged activation of already excited neurons and associated burst firing.

Calcium entry may also ultimately result in excitotoxicity and cell death.Excitatoryaminoacidsare also able to interact with metabotropic receptors that activate second messenger systems to influence biochemical pathways and ion channels.These receptors are found both presynaptically and postsynaptically.Activation usually results in presynaptic inhibition and

postsynaptic excitation.These receptors may have an important role in supporting epileptic activity.

ACETYLCHOLINE RECEPTORS[33]:

They serve as ligand gated sodium channels.Mutation of a gene,CHRNA4,which encodes for the beta2 sub unit of the receptor has been associated with autosomal dominant frontal lobe epilepsy.

EPILEPTIC ACTIVITY IN NEURONAL SYSTEMS:

While molecular changes may predispose to burst firing of neurons,synchronization of such activity,necessary for seizures also require the involvement of neuronal circuits.

FOCAL EPILEPTOGENESIS:

The most studied and clinically relevant model of focal seizures and epileptogenesis is the hippocampus and hippocampal sclerosis, is the most common form of focal epilepsy in man.Mesial temporal structures are interconnected by a reverberating loop involving entorhinalcortex,dentate gyrus,CA3,CA1pyramidal neurons.Normal spontaneous activity of CA3pyramidal neurons consists of paroxysmal depolarization shifts and associated burst firing of the cell body and apicaldendrites.In normal brain, bursting activity in CA3 neurons

will evoke, bursts in connected neurons(30%)[34].This probably increases when the pyramidal cell is excited by many inputs simultaneously.Three phenomena implicated.Cellloss,Mossy fibre sprouting and Neurogenesis may all enhance the potential for seizure generation while resulting in pathological change that can lead to hippocampal sclerosis.In the kindling model of epilepsy, repeated sub-convulsive electrical stimulation,usually to the amygdale leads to increasing after discharge and ultimately to behavioural seizures.

It appears that limbic structures are particularly sensitive to the development of kindling when compared to neocortex, a situation that is reflected in man,where the temporal lobe is by far the most common site of seizure onset.In the pilocarpine model of chronic epilepsy, seizures can induce neurogenesis,neurons being abnormally integrated into existing circuits.These changes therefore provide a potential basis for the clinical predisposition of the mesial temporal structure to produce seizures and a plausible mechanism for some of the progressive changes that may be seen as part of drug-resistant epilepsies.

GENERALISED EPILEPSIES:

In generalised epilepsies, there will be a very generalised disturbance of neuronal activity in both hemispheres.2 schools of thought exist.One study specifies that , it is primarily a cortical process. In an another study, there is an unspecified

centrencephalic system in which structures of the upper brainstem and thalamus are responsible for generating the spike wave discharge and driving a cortical synchrony[34]exists.

The cellular substrate for these phenomena is now well understood.It is dependent on a thalamocortical circuit that includes the nucleus reticularisthalami.The circuits involve excitatory glutaminergic synapses and inhibitory gabanergicsynapses.The behaviour of thalamic neurons and the circuit is largely determined by the presence of a high density of calcium channels,which results in Ca2/k dependent burstfiring.Theseinturn can give rise to strong inhibitory postsynaptic potentials mediated by GABAb receptors in thalamo cortical relay neurons[34].

This circuitry is important in activating cortical neurons during sleep-waking cycles.Tonic activity in the relay neuron occurs during wakefulness and during rapid eye movement sleep,but they fire in the burst mode during NREM sleep[39].During drowsiness and sleep, thalamic neurons hyperpolarize and begin to exhibit typical repetitive burst firing that contributes to sleep spindles in the EEG.The classic anti-absence drug ethosuximide acts by causing a voltage dependent blockade of T-type calcium currents, a property shared by valproate.Hyperpolarization and burst firing is greatly facilitated by GABAnergic activity via GABAbmechanisms.

METHODS AND MATERIALS

METHODS AND MATERIALS

The present study had been conducted at Government RajajiHospital,Madurai Medical College,Madurai during the period between March 2012 and February2013.I have obtained written consent from the patient, after explaining about the study in detail. I got the ethical committee clearance, for this study from Madurai Medical College,Madurai. The outpatients registered at the Epilepsy clinic, Government Rajaji Hospital, Madurai Medical college during a one year period between March2012 and February2013 were taken up for the study. The clinical details were obtained from the epilepsy clinicoutpatient register/case sheets and patient interviews with the help of the priorly prepared proforma.I have taken details on demographic profile,seizure history and treatment history by interviewing the patient and from the case history with the help of standard questionnaire. I have asked the patients, torecord the seizure and headache occurrencedetails in a diary. Associated symptoms, as well asprecipitating factors for the headache will be noted by them.The diary will be scrutinizedmonthlyduring the period of the survey. Headache Impact Test (HIT-6) would be done to assess the headache impact in patient's daily life.

Study Design:

Prospective cross sectional observation study.

Period of study:

March 2012 to February 2013.

Study population:

300 epileptic patients who attended the Epilepsy Outpatient Clinic, GovernmentRajaji Hospital, Madurai Medical College between March2012 an February 2013.

Inclusion criteria:

1.Patients registered at the Epilepsy outpatient clinic, GovernmentRajajiHospital,Madurai.

2. Known Patients with Primary Generalised Epilepsy.

3. Agreed to participate in the study.

4.More than 12 years of age.

Exclusion criteria:

1.Patient's refusal to participate in the study.

2.Patients having nonepilepticattacks, symptomatic fits like metabolic causes,toxins induced and meningoencephalitis.

3.Patients with neurodevelopmental disorders.

4.Mentally challenged persons,patients on antipsychotics.

5.Pregnancy and CNS malignancy.

6.Focal seizures.

7.Patients already on prophylactic drugs for headache.

8.Epileptic patients on tablet sodium valproate.

Definitions:

Seizure and the epileptic syndromes were classified according to the guidelines of ILAE.

Preictal headache:

It is defined as the headache which occurs ≥30 mts prior to the seizure andcontinuedtill the seizure onset.

Ictal Headache:

It occurs simultaneously with the seizure onset and postictal headache occurs immediately after the stoppage of seizure event.

Periictal headache:

Periictal headache is the combination of headache which occurs during preictal, ictal and in the immediate postictal state.

Interictalheadache:

Those headaches which occur during theInterictal period and the headache will not be related directly to the seizure. The Headache was classified based on the patient's statement.

CALCULATION OFSAMPLE SIZEAND ANALYSIS OF STATISTICS:

Around 300 patients with known primary generalised epilepsy were followed up over a one year period between March2012 and February2013, who attended the epilepsy outpatient clinic.P-value of<0.05 was consideredsignificant statistical value to correct for the multiple comparisons. SPSS13.0 is used for statistical analysis.

RESULTS AND ANALYSIS

RESULTS AND ANALYSIS

In the present study which was conducted over 1year observation period, totally 248 patients(out of 300 recruited) completed the study and they were analysed . Their mean age was 36.30years and 123(49.60%) of them were female, and 125 were male (50.40%)(Table 1). Average duration of seizure disorder was 6.52yrs.The total number of patients developed headache was 72(29%) and without headache was 176(70.97%)(Table2).Of the 72 patients developed headache, 27 were male and 45 were female patients.(Table3)

Among the 72(29%) patients with headache,54(21.7%) patients developed headache in the interictal period and 10(4.03%) in the periictal period and 8(3.22%) patients developed headache both in the periictal as well as in the interictal period(Table4). 27(10.9%) Patients had developed migraine type of headache and 20(8.06%)patients had tension type headache and 25(10.08%) patients developed nonspecific headache. In the present study, this reveals that migraine is the most common type of headache in patients suffering from epilepsy,.In the interictal period,21 patients developed tension type of headache and 17 had developed migraine headache & 16 patients developed tension type of headache .This showed that patients with nonspecific headache predominates in the interictal period.(Table5)

Among the 10 patients developed headache in the interictal period 5 had migraine without aura and 2 developed tension type headache & 3patients presented with nonspecific headache.8 patients developed headache bothin the interictal and periictalperiod.Of them,4 had migraine with aura and 1 developed migraine without aura & 2patients developed tension type headache ,1patient had nonspecific headache.This also showed, that patients with migraine headache predominated the periictal period as well as the periictal+interictal period, in the present study.

TOTAL HEADACHE EPISODES IN THE STUDY PERIOD:

72 patients developed 223 headache episodes during the study period. Among the 223 headache episodes ,the migraine with aura was 52, migraine without aura was 39 and tension type of headaches were 63 and nonspecific headache episodes were 69(p-value 0.117).In the present study, the migraine type of headache occurred in large number followed by tension type headache and nonspecific headache. In the periictal period, the total number of headache episodes, the patients developed was 52. Among the 52 headaches, the migraine headache episodes were 31, tension type of headache was 11 and 10 nonspecific headache episodes.p-value for this is 0.004 which is statistically significant value. This reveals that migraine is the most frequent type of headache in the periictal period.(Table8)

HEADACHE OCCURRENCE IN RELATION TO SEIZURE FREQUENCY: (Table9)

Among the 158 patients, with seizure frequency of >3per month, 60(37.97%) patients developed headache. Total number of patients with seizure frequency of 1-3 per month is 60. Among the 60 patients, 10(16.66%) patients developed headache. Among the 30 patients with seizure frequency of 0-1 per month, 2 (6.66%) patients developed headache. The present study showed that, the incidence of headache increases whenever the seizure frequency also increases, from 6.66%(0-1seizure/month)and 16.66%(1-3seizure/month) to 37.97%(>3seizure/month) and clearly reveals the relation between the headache occurrence with the number of seizure episodes. The p-value for this, is 0.005 which is statistically significant.

HIT Score :(Table10)

In the present study,72 patients developed various headaches .Among the 72 patients with headache, 36(50%) patients showed very severe impact in HIT score and 16 (22.22%) patients developed, little or no impact in their life, due to headache.The p-value for this is 0.026 which is statistically significant.HIT score reveals that the headache influenced most of the patient's daily life negatively.

Seizure frequency per month:

•Total no of patients→ 248

•No of patients with >3 episode/ month→158

• 1-3 episode/month→60

•0-1 episode /month→30

The average seizure frequency was 9.09 during the study period.

No of patients developed headache during the study:

Total no of patients with headache→72 (29%)

•Male→27 (10.88%)

•Female→45 (18.14%)

No of patients with headache, in relation to seizure event:

•Total no of patients with headache→ 72(29%)

•No ofpatients with Interictal headache→54 (21.7%)

•No of patients with periictal headache→10 (4.03%)

•No of patients with both interictalplusperiictal headache→8 (3.22%)

The average headache episode per person was 3.09 duringthe study period.

Total no of patients with headache 72 :(Table 3)

Types:

1.Migraine headache→ 27(10.88%)

•Migraine with aura→14 (5.64%)

•Migraine without aura→13 (5.24%)

2. Tension headache→20 (8.06%)

3. Non specific headache→25 (10.08%)

TOTAL NUMBER OF HEADACHE EPISODES→223 (Table 6)

•Interictal headache→171

•Periictal headache→52

Total no of headache episode : 223(Table7)

•Migraine with aura→52

•Migraine without aura→39

•Tension type headache→63

•Nonspecific headache→69

Total no of Interictal headache: 171

•Migraine with aura →38

•Migraine without aura→22

•Tension type headache→52

•Nonspecific headache→59

Total no of Periictal headache episode: 52

•Migraine with aura→14

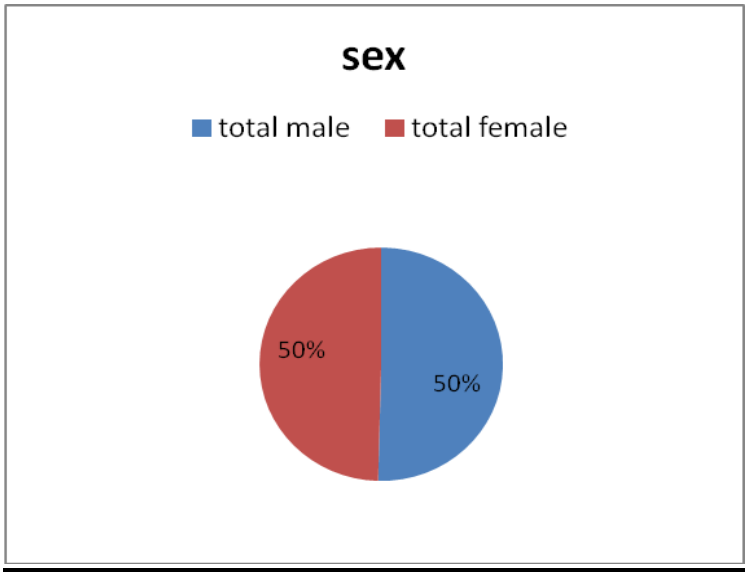
•Migraine without aura→17

•Tension type headache →11

•Nonspecific headache→10

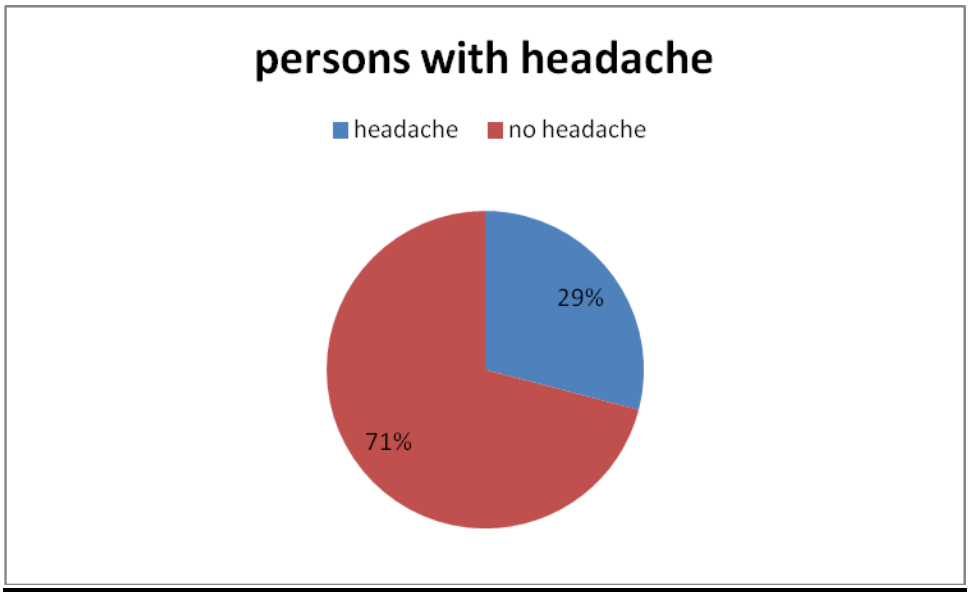
SEX DISTRIBUTION [TABLE 1]

total male	125	50.40%
total female	123	49.60%
	248	



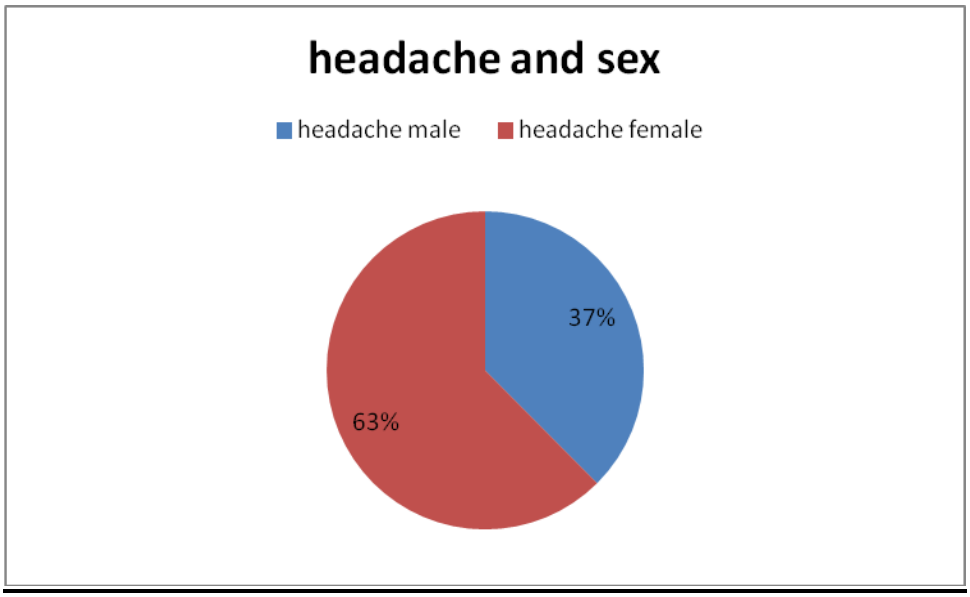
NUMBER OF PERSONS WITH HEADACHE [TABLE 2]

headache	72	29%
no headache	176	70.97%
	248	



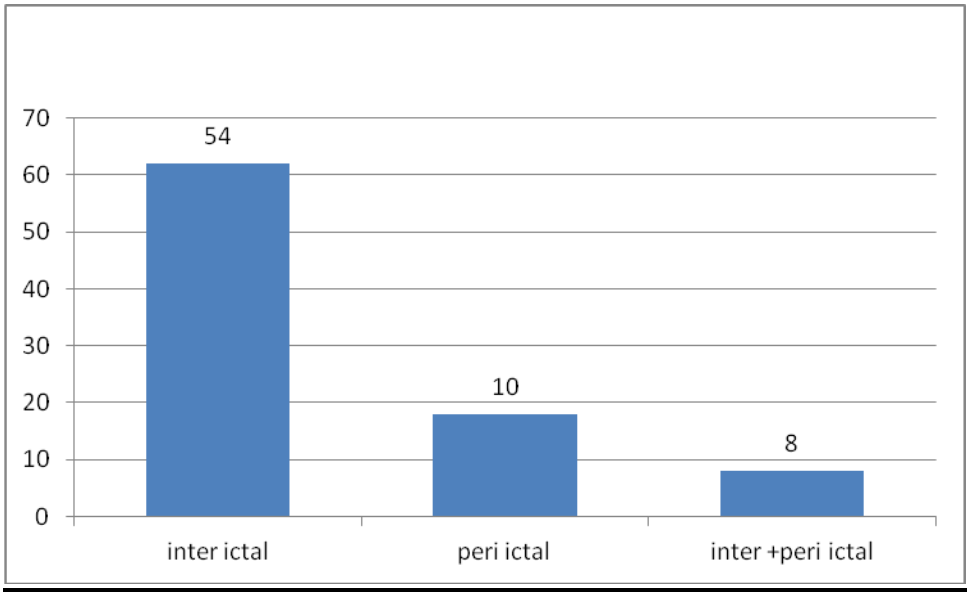
NUMBER OF PERSONS WITH HEADACHE IN RELATION WITH SEX [TABLE 3]

headache male	27	
headache female	45	
	72	29.00%



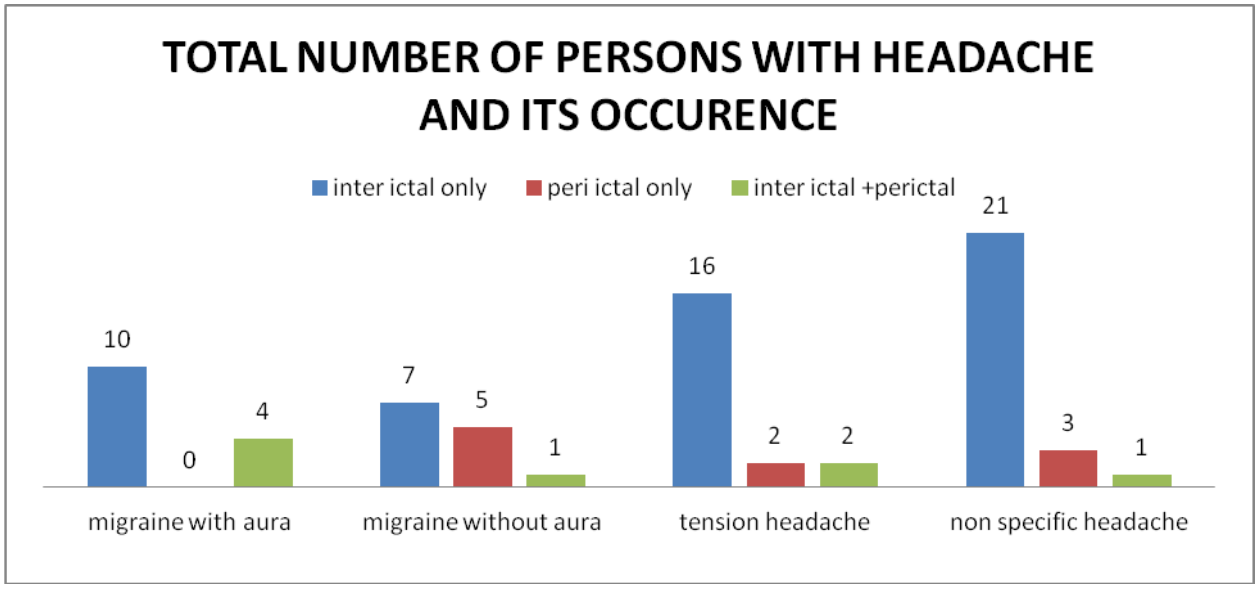
NUMBER OF PATIENTS WITH HEADACHEIN RELATION TO SEIZURE PERIOD [TABLE 4]

Seizure period	Number of persons with headache	among total
inter ictal	54	21.7%
periictal	10	4.03%
inter +periictal	8	3.22%



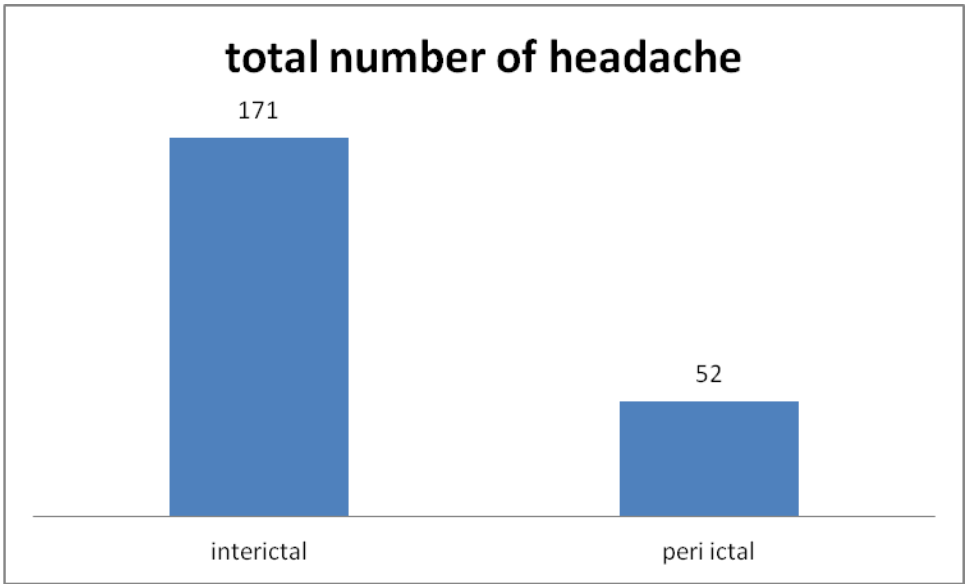
NUMBER OF PATIENTS WITH HEADACHE IN RELATION TO SEIZURE [TABLE 5]

type of headache	inter ictal only	periictal only	inter ictal +perictal	total	among total pts
migraine with aura	10	0	4	14	5.64%
migraine without aura	7	5	1	13	5.24%
tension headache	16	2	2	20	8.06%
non specific headache	21	3	1	25	10.08%
total	54	10	8	72	



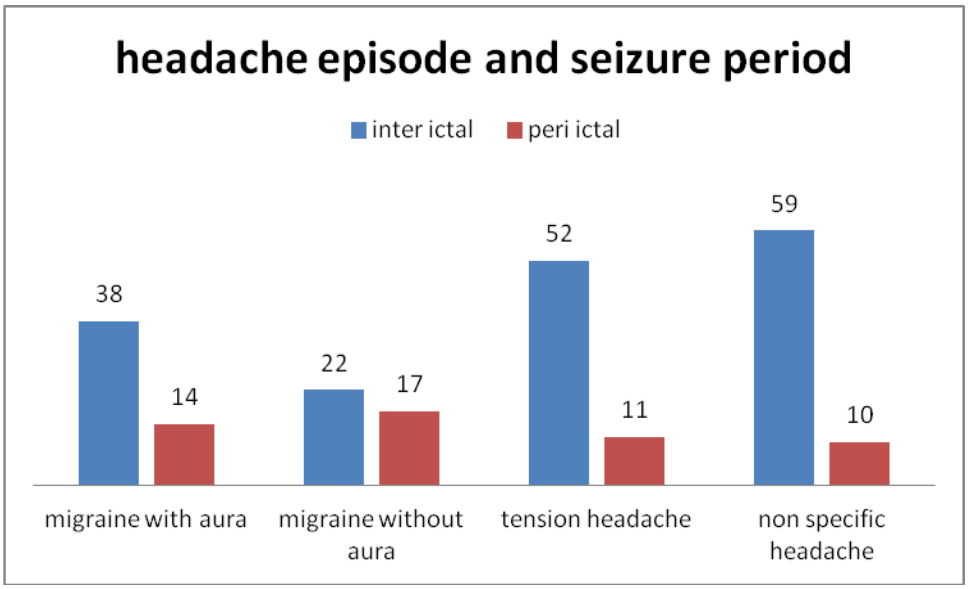
TOTAL NUMBER OF HEADACHE EPISODES [TABLE 6]

interictal	171
periictal	52



NUMBER OF HEADACHE EPISODE IN RELATION TO SEIZURE PERIOD [TABLE 7]

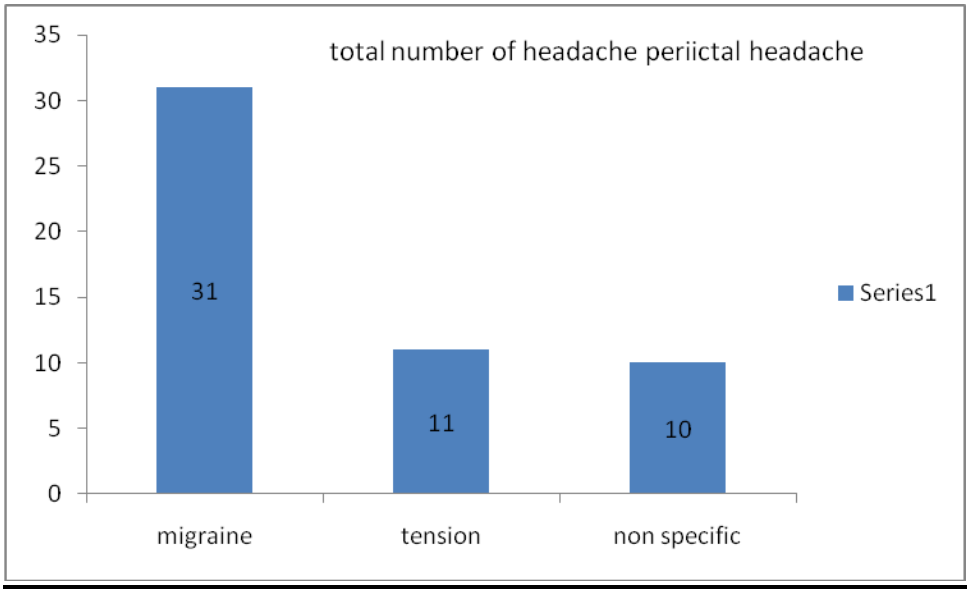
type of headache	inter ictal	periictal
migraine with aura	38	14
migraine without aura	22	17
tension headache	52	11
non specific headache	59	10
total	171	52



TOTAL NUMBER OF HEADACHE IN PERIICTAL PERIOD [TABLE 8]

migraine	31
tension	11
non specific	10
total	52

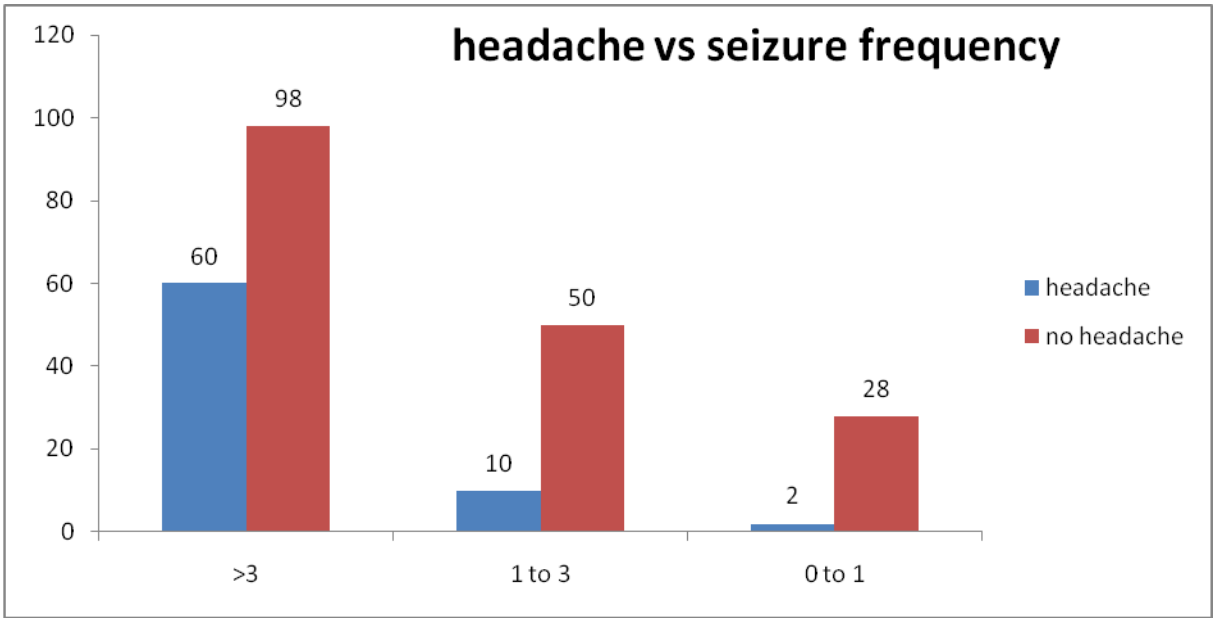
p value = 0.004



NUMBER OF PERSONS WITH HEADACHE IN RELATION TO SEIZURE FREQUENCY [TABLE 9]

Seizure frequency/month	headache	no headache	total
>3	60	98	158
1-3	10	50	60
0-1	2	28	30
total	72	176	248

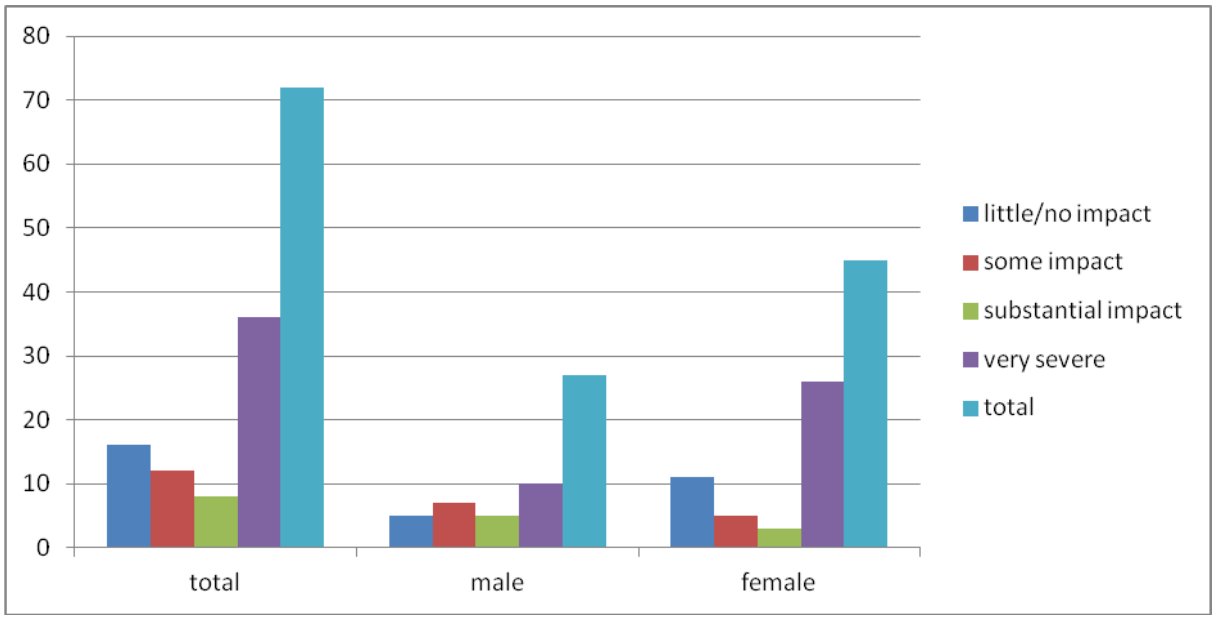
p value= 0.005



HIT (HEADACHE IMPACT TEST) SCORE [TABLE 10]

category	total	male	female
little/no impact	16	5	11
some impact	12	7	5
substantial impact	8	5	3
very severe	36	10	26
total	72	27	45

P value=0.026



DISCUSSION

DISCUSSION

Epilepsy and Migraine are the chronic disorders with recurrent neurological dysfunction associated with headache and autonomic, abdominal and psychotic features. In some patients it may be difficult to differentiate between migraine and the seizure episodes. Both are having comorbid symptoms and occurrence. The present study had been conducted at Government Rajaji Hospital, Madurai Medical College, Madurai during the period between March 2012 and February 2013.

In the present study which was conducted over 1year observation period, totally 248 patients(out of 300 recruited) completed the study and they were analysed . Their mean age was 36.30years and 123(49.60%) of them were female, and 125 were male (50.40%). Average duration of seizure disorder was 6.52yrs .In the previous study by P.Kwan et al[2], totally around 306 patients with epilepsy were recruited and 227 of them completed the study. The mean age was 36 years and 98(43.2%) of them were female and 129(56.8%) were male patients. The mean duration of epilepsy in the study group was 16years.

In the Multicenter study from HELP (Headache in Epileptic Patients)[3] group study, 597 patients with epilepsy were recruited. The mean age was 34.9years and 348(58.3%) of them were female and 249(41.7%) were male patients. The mean

duration of epilepsy in the study group was 8years.The data of the present study were closer with P.Kwan et al study and Multicenter study from HELP group.

In the current study,the total number of patients developed headache was 72(29%) and without headache was 176(70.97%).Of the 72 patients developed headache, 27 were male and 45 were female patients. InP.Kwan et al study, the total no of patients with headache was 50(22%) and without headache was 77(78%) and in HELP group study the total no of patients with headache was 169(28.3%) and without headache was 428(71.69%).

In the present study,54 (21.7%) patients developed Interictal headache and 10(4.03%) patients developed periictal headache and 8(3.22%) patients developed, headache in both periictal and in the interictalperiod.This data was consistent with the study from P.Kwan and Multicenter study group.InP.Kwan study, 45(19.8%) patients developed headache in interictal period and 11(4.8%) patients developed periictal headache &5(2.2%) patients developed headache both in interictal as well as in the periictal period.

In the Multicenter study group,146(24.4%) patients developed headache in interictal period and 35(5.9%) patients developed periictal headache.

INCIDENCE OF MIGRAINE IN SEVERAL STUDY GROUPS:

1. In the present study→10.9%

2. InMulticenter study group→12.4%

3. InP.Kwan et al study group→7.92%

4. In Korean study group[5]→6.5%

Our study results were consistent with other studies.Migraine prevalence in most of the studies was 8-20%.

NO OF PATIENTS WITH MIGRAINE IN PERIICTAL PERIOD:

In the Present study→50%

In Multicenter study group→46.2%

In Yankovsky et al study[12]→36%

In Leniger et al study[8]→56%

The percentage of migraine patients intheperiictal period was similar to other studies.33% of patients with Interictal headache, had developed migraine type of headache which is closer to P.Kwan study, where 23% of patients in the Interictal period, developed migraine typeof headache.

In the present study 27(10.9%) patients developed migraine headache and in Multicenter study group, 74(12.4%) developed migraine and in the P.Kwanstudy 18(7.9%) had migraine attacks.

HEADACHE OCCURRENCE WITHTHE SEIZURE FREQUENCY: Among the 158 patients, with seizure frequency of >3per month, 60(37.97%) patients developed headache. Total number of patients with seizure frequency of 1-3 per month is 60. Among the 60 patients, 10(16.66%) patients developed headache. Among the 30 patients with seizure frequency of 0-1 per month, 2 (6.66%) patients developed headache. The present study showed that, the incidence of headache increases whenever the seizure frequency also increases, from 6.66%(0-1seizure/month)and 16.66%(1-3seizure/month) to 37.97%(>3seizure/month) and clearly reveals the relation between the headache occurrence with the number of seizure episodes. The p-value for this, is 0.005 which is statistically significant.

But in most of the other studies (Leniger et al[8], Forderreuther et al[7] Karaali-Savrun et al[9]) there was no specific association of headache and seizure frequency was noted. In the present study, 29% of patients with primary generalised epilepsy haddeveloped migraine headache but in Multicenter study[3] there wasno such

correlation, but 30-50% of the patients with occipital lobe epilepsy developed migraine with aura as a predominant seizure related headache.

Cortical spreading depression considered to be the mechanism of migraine aura, and characterised by transient increases in the metabolic and electrical activity & cerebral blood flow, followed by sustained decreases, spreading from the posterior to anterior cerebral area. Therefore the occipital lobe could be the brain structure most responsible for the development of migraine. Migraine, seizure related headache might be more likely to occur in association with occipital lobe epilepsy.

HIT SCORE AND ITS IMPACT ON PATIENT'S DAILY LIFE:

In the present study,72 patients developed various headaches .Among the 72 patients with headache, 36(50%) patients showed very severe impact in HIT score and 16 (22.22%) patients developed, little or no impact in their life, due to headache.The p-value for this is 0.026 which is statistically significant.HIT score reveals that the headache influenced most of the patient's daily life negatively.In P.Kwan et al[2] study,34% of the patients with headache developed very severe impact in their life.

The current study measured the incidence of headache, in epileptic patients prospectively. In this study nonepileptic patients, as control have not included for direct comparison of incidenceof headache between the patients and the common

population. In a prior, communitybased retrospective survey, patients recalled their headacheforaprolongedperiodand 37.2% of them developedheadache. Control group might be added in future studies. This study showed the incidence of headache in relation to the seizure frequency. This might help the statistical capacity to analyze other things whichmay be associated with headache, like epilepsy syndrome, typeof seizure& antiepileptic drug details.

This study suggests that Migraine is a frequent comorbid disorder in patients with epilepsy and an important factor which affects the occurrence and type of seizure related headache.

This study also demonstrates that seizure related headache is a common accompanying symptom of seizure, causes major impairment in daily life. The links between the epilepsy, seizure related headache and migraine are an important subject for future investigation.

Headache is under diagnosed mostly,inspiteof the lower incidence in this study. The headache interferes the patient's lifestyle and influenced his life negatively. So we have to give more importance, in the diagnosis of headache even with patients having low frequency of seizure episode. Large studies with more number of patients, control group are required for the risk factor identification and to evaluate the treatment strategies to reduce its impact.

SUMMARY

SUMMARY

•Total duration of observational study period →1year

•Total no of patients studied→248

•Total no of patients with headache→ 72 (29%)

•Total no of patients with Interictal headache→54 (21.7%)

•Total no of patients with periictal headache→10 (4.03%)

•Total no of patients with both interictalplusperiictal headache→8 (3.22%)

The average headache episode per person was 3.09 duringthe study period.

Total no of patients with headache 72:

Patients with Headache:

1. Migraine headache→ 27(10.88%)

•Migraine with aura→14 (5.64%)

•Migraine without aura→13 (5.24%)

2. Tension headache→20 (8.06%)

3. Non specific headache→25 (10.08%)

In the present study,patientswith migraine headache predominated theother type of headache like, tension type headache and other nonspecific headache. The frequency of migraine is more in the periictal period than in the Interictal period.

HEADACHE INCIDENCE VERSUS SEIZURE FREQUENCY:

The present study showed that incidence of headache increases, whenever the seizure frequency also increases, from 6.66%(0-1seizure/month) and 16.66%(1-3seizure/month) to 37.97%(> 3seizure/month) and clearly reveals the relationship between the headache occurrence with the number of seizure episodes per month. The p-value for the current study is 0.005 which is statistically significant.

HIT SCORE AND ITS IMPACT ON PATIENT'S LIFE:

In the present study,72 patients developed various headaches .Among the 72 patients with headache, 36(50%) patients showed very severe impact in HIT score and 16 (22.22%) patients developed, little or no impact in their life, due to headache.The p-value for this is 0.026 which is statistically significant.HIT score reveals that the headache influenced most of the patient's daily life negatively.

CONCLUSION

CONCLUSION

1.The present study showed the incidence of headache among the epileptic patients and its impact on their daily life.

2.In the present study, the headache incidence increases with the seizure frequency,whichreiterates thefactthat,adequate seizure control is essential to reduce the incidenceof headache inpatients with epilepsy.

3.Headache incidence in epileptic patients can be considerably ameliorated by choosing appropriate drug that will be useful for both seizure and headache.

4. This study demonstrates (HIT score) that seizure related headache is a common accompanying symptom of seizure, causes major impairment in daily life. Hence, by reducing the incidence of headache, we can improve the quality of life in patients with epilepsy.

5.This study also suggests that migraine is a frequent comorbid disorder in patients with epilepsy and an important factor which affects the occurrence and type of seizure related headache.

6 The links between the epilepsy, seizure related headache and migraine are an important subject for future investigation.

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STUDY PROFORMA

Name :

Age/sex :

OP No :

Chief complaint :

Duration of Epilepsy :

Seizure occurrence :

Type of Headache :

Duration of Headache :

RelationshipofHeadachewith Epilepsy:

Treatment details :

Type of Headache :

Female patients-pregnant(yes/no) :

Associated fever and Headache with seizures-To rule out CNS infection:

Previous H/O intracranial space occupying lesion:

Previous H/O psychiatric illness or antipsychotic intake:

HEADACHE IMPACT TEST QUESTIONNAIRE

Name:_____ Date:_____

Please circle the response that best describes how you feel and calculate the totals below.

1. When you have headaches, how often is the pain severe?

A) Never B) Rarely C) Sometimes D) Very Often E) Always

2. How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?

A) Never B) Rarely C) Sometimes D) Very Often E) Always

3. When your have a headache, how often do you wish you could lie down?

A) Never B) Rarely C) Sometimes D) Very Often E) Always

4. In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?

A) Never B) Rarely C) Sometimes D) Very Often E) Always

5. In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?

A) Never B) Rarely C) Sometimes D) Very Often E) Always

6. In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?

A) Never B) Rarely C) Sometimes D) Very Often E) Always

# of A's
Multiply by 6 points each

# of B's
Multiply by 8 points each

# of C's
Multiply by 10 points each

# of D's
Multiply by 11 points each

# of E's
Multiply by 13 points each

Note: # = Number

HIT-6 score :

Bonus Questions
On a scale of 0-10, with "10" being the worst discomfort imaginable above the shoulders, and a "0" is no
pain at all (you feel fabulous), how many mornings per week do you wake with a "0", that is, *you feel fabulous?*_____
On those mornings that you wake "with a number", what's the average number that you have?
_____

Your headaches are having a very severe impact on your life. You may be experiencing disabling pain and other symptoms that
are more severe than those of other headache sufferers. Don't let your headaches stop you from enjoying the important things in
your life, like family, work, school or social activities.
Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 56 – 59
Your headaches are having a substantial impact on your life. As a result you may be experiencing severe pain and other

symptoms, causing you to miss some time from family, work, school, or social activities.
Make an appointment **today** to discuss your HIT-6 results and your headaches with your doctor.

If You Scored 50 – 55
Your headaches seem to be having some impact on your life. Your headaches should not make you miss time from family,
work, school, or social activities.
Make sure you discuss your HIT-6 results and your headaches at your next appointment with your doctor.

If You Scored 49 or Less

Your headaches seem to be having little to no impact on your life at this time. We encourage you to take HIT-6 monthly to
continue to track how your headaches affect your life.

If Your Score on HIT-6 is 50 or Higher

You should share the results with your doctor. Headaches that are disrupting your life could be migraine.

MASTER CHART

s.no	age	sex	seizure duration	headache	no of headache	seizure episodes per month			seizure associated headache			types of headache				HIT
						>3	1 to3	0 to 1	inter only	peri only	inter+peri	m + a	m - a	ten	ns	
1	45	f	3	0	-		1	1								-
2	23	m	7	0	-			1								-
3	43	m	2	0	-			1								-
4	32	f	8	1	3	1			1					1		63
5	45	f	3	0	-		1	1								-
6	23	m	8	1	1	1				1			1			62
7	21	f	2	0	-			1								-
8	43	m	6	0	-		1	1								-
9	56	f	1	1	4	1			1			1				57
10	34	f	8	0	-			1								-
11	21	m	3	0	-		1	1								-
12	35	f	8	0	-			1								-
13	67	m	1	0	-		1									-
14	53	f	7	0	-		1	1								-
15	63	m	1	1	3	1			1					1		46
16	56	f	7	1	4	1			1						1	53
17	43	f	1	0	-		1	1								-
18	46	f	4	0	-		1									-
19	37	m	8	0	-		1	1								-
20	35	f	1	0	-		1									-

21	27	m	2	1	3	1			1			1				48
22	26	m	7	0	-		1									-
23	35	f	1	0	-		1	1								-
24	37	m	5	0	-		1	1								-
25	36	f	2	1	3	1				1			1			64
26	36	f	1	1	2	1			1					1		62
27	27	f	8	0	-		1									-
28	27	m	6	0	-		1									-
29	24	f	4	0	-		1									-
30	35	m	2	1	4	1			1			1				47
31	17	f	1	1	3	1				1					1	43
32	32	m	8	0	-		1									-
33	53	m	7	0	-		1									-
34	46	m	3	1	3	1			1					1		48
35	35	m	7	0	-		1									-
36	23	f	4	1	3	1			1						1	41
37	43	m	8	0	-		1									-
38	57	f	5	0	-		1	1								-
39	45	m	8	0	-		1									-
40	43	f	7	0	-		1	1								-
41	36	m	3	0	-		1									-
42	25	f	5	0	-		1	1								-
43	43	m	6	1	6			1	1				1			52
44	35	m	4	0	-		1									-
45	25	m	7	0	-											-
46	43	f	9	1	5		1		1					1		64
47	44	f	6	0	-											-

48	45	f	8	1	4	1				1					1	44
49	36	m	5	0	-		1									-
50	42	m	7	0	-											-
51	36	m	4	1	2	1			1					1		60
52	43	m	7	0	-											-
53	36	f	8	0	-		1									-
54	17	m	4	0	-			1								-
55	32	f	5	1	2	1			1						1	63
56	54	f	6	0	-											-
57	26	f	8	1	3	1					1	1				57
58	43	m	4	0	-											-
59	35	f	9	1	2	1			1					1		41
60	25	f	6	0	-											-
61	43	m	8	0	-		1									-
62	27	m	5	1	3	1				1					1	46
63	26	m	7	0	-											-
64	24	f	4	0	-		1									-
65	23	m	8	0	-											-
66	34	f	7	1	2	1			1						1	53
67	42	m	6	0	-		1									-
68	36	m	9	1	4	1			1					1		59
69	32	f	4	0	-											-
70	45	m	7	0	-											-
71	23	m	5	0	-											-
72	34	f	8	0	-											-
73	45	f	2	1	3	1			1				1			63
74	54	m	7	0	-	1										-

75	43	f	3	1	3	1			1					1		41
76	32	f	9	0	-			1								-
77	26	f	6	1	5		1		1						1	42
78	45	m	7	0	-			1								-
79	43	f	5	1	3	1			1					1		65
80	32	f	3	0	-			1								-
81	26	m	6	0	-		1									-
82	43	m	8	1	4	1			1					1		54
83	35	f	5	0	-		1									-
84	25	m	7	0	-		1	1								-
85	45	m	3	0	-		1									-
86	36	f	8	0	-		1									-
87	33	m	6	1	2	1			1			1				61
88	24	f	4	0	-		1									-
89	44	m	7	0	-		1									-
90	26	f	9	1	2	1			1				1			42
91	21	f	6	0	-		1									-
92	36	m	7	0	-		1									-
93	45	m	5	1	3	1			1						1	48
94	26	f	9	0	-		1									-
95	36	m	6	0	-			1								-
96	42	m	5	1	4	1				1			1			46
97	26	f	7	0	-			1								-
98	26	f	8	1	1	1			1						1	58
99	43	m	6	0	-			1								-
100	36	f	9	0	-			1								-
101	42	f	5	1	2	1			1						1	53

102	36	f	4	0	-			1								-
103	15	m	8	0	-			1								-
104	36	f	8	1	5		1		1						1	59
105	42	f	6	0	-		1									-
106	36	m	9	0	-		1									-
107	25	m	7	1	4	1			1						1	58
108	41	f	4	0	-		1									-
109	37	m	7	0	-		1									-
110	52	m	8	0	-		1									-
111	43	f	6	0	-		1									-
112	42	m	8	0	-	1										-
113	27	m	5	0	-		1									-
114	41	f	4	0	-		1									-
115	37	f	9	1	3	1			1					1		63
116	26	f	5	0	-		1									-
117	31	m	9	0	-	1										-
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122	35	f	4	0	-	1										-
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125	68	f	9	1	4	1				1				1		54
126	46	f	6	0	-	1										-
127	36	m	2	0	-	1										-
128	24	f	10	0	-	1										-

129	23	m	9	1	1	1			1			1				47
130	34	f	7	0	-	1										-
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132	36	m	5	0	-	1										-
133	42	m	14	1	3	1			1						1	48
134	43	f	9	0	-	1										-
135	47	m	8	0	-	1										-
136	27	m	5	0	-	1										-
137	43	f	7	1	4	1			1					1		57
138	37	f	4	0	-	1										-
139	32	m	6	0	-	1										-
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141	37	m	7	1	2	1			1					1		57
142	25	f	5	0	-	1										-
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150	35	m	8	0	-	1										-
151	25	f	5	1	3	1					1	1				54
152	37	f	3	0	-	1										-
153	34	m	6	0	-	1										-
154	35	m	4	1	2	1			1						1	54
155	36	f	8	0	-	1										-

156	32	m	9	0	-	1										-
157	34	f	7	1	3	1				1			1			62
158	26	f	8	0	-	1										-
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162	32	f	8	0	-	1										-
163	34	m	5	0	-	1										-
164	42	f	7	1	1	1					1			1		43
165	26	f	6	0	-	1										-
166	37	m	4	0	-	1										-
167	27	f	2	1	4		1		1						1	53
168	24	f	8	0	-	1										-
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170	27	f	9	1	7		1				1	1				57
171	23	f	6	0	-	1										-
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174	47	f	4	1	2	1			1			1				41
175	45	f	6	0	-	1										-
176	38	m	2	0	-	1										-
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179	46	m	4	0	-	1										-
180	26	f	8	0	-	1										-
181	44	f	6	1	3	1			1				1			42
182	36	m	2	0	-	1										-

183	36	m	1	0	-	1										-
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186	38	f	5	0	-	1										-
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189	49	f	8	0	-	1										-
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191	37	m	9	1	2	1			1						1	57
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208	43	f	13	0	-	1										-
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210	25	f	7	0	-	1										-
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227	26	m	7	0	-	1										-
228	48	m	9	1	5			1			1	1				48
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231	47	f	4	1	2	1			1				1			58
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246	24	m	4	0	-	1										-
247	43	m	10	0	-	1										-
248	35	m	12	0	-	1										-
				1=presence		1 = presence										

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Institutional Review Board / Independent Ethics Committee.
Dr. N. Mohan, M.S., F.I.C.S., F.A.I.S.,
Dean, Madurai Medical College &
Govt Rajaji Hospital, Madurai- 625020.
Convenor
grhethicssecy @gmail.com.

Sub: Establishment-Govt. Rajaji Hospital, Madurai-20-
Ethics committee Meeting- approval -regarding.

The Ethics Committee meeting of the Govt. Rajaji Hospital, Madurai was held at 10.00 am to 12.30.Pm on 10.12.2012 at the Surgery Seminar Hall, Govt. Rajaji Hospital, Madurai. The following members of the committee have attended the meeting.

1.Dr. V. Nagarajan, M.D., D.M (Neuro) Ph: 0452-2629629 Cell.No 9843052029	Professor of Neurology (Retired) D.No.72, Vakkil New Street, Simmakkal, Madurai -1	Chairman
2. Dr.Mohan Prasad , M.S M.Ch Cell.No.9843050822 (Oncology)	Professor & H.O.D of Medical Oncology(Retired) D.No.72, West Avani Moola Street, Madurai -1	Member Secretary
3. Dr.L. Santhana Lakshmi,MD Cell.No 9842593412	Associate Professor of Physiology/V.P Madurai Medical College	Member
4. Dr. Parameswari M.D (Pharmacology) Cell.No.9994026056	Director of Pharmacology Madurai Medical College	Member
5. Dr.Moses K.Daniel MD(Gen.Medicine) Cell.No 09842156066	Professor & H.O.D of Medicine Madurai Medical College	Member
6. Dr.D. Soundara Rajan,MS(Gen.Surgery) Cell.No 9842120127	Professor & H.O.D of Surgery Madurai Medical College	Member
7. Dr.Angayarkanni MD(O&G) Cell.No 9443567724	Professor & H.O.D of O&G Madurai Medical College	Member
8. Dr.P.V. Pugalenthi M.S, (Ortho) Cell.No 9443725840	Professor & H.O.D Ortho Madurai Medical College	Member
9. Dr. M. Sundarajan M.S., Mch Cell.No 9994924369 (Neuro Surgery)	Professor (Neuro Surgery) Madurai Medical College	Member
10 Thiru..Pala. .Ramasamy , BA.,B.L., Cell.No 9842165127	Advocate, D.No.72.Palam Station Road, Sellur, Madurai -2	Member
11. Thiru. P.K.M. Chelliah ,B.A Cell.No 9894349599	Businessman, 21 Jawahar Street, Gandhi Nagar, Madurai-20.	Member

The following Project was approved by the committee

Name of P.G.	Course	Name of the Project	Remarks
Dr. Suresh Khanna.	PG in D.M (Neurology), Govt. Rajaji Hospital & Madurai Medical College.	Clinical Evaluation of Migraine and other seizure Related Headaches in Patients with epilepsy.	Approved

Please note that the investigator should adhere the following: She/He should get a detailed informed consent from the patients/participants and maintain Confidentially.

1. She/He should carry out the work without detrimental to regular activities as well as without extra expenditure to the institution to Government.
2. She/He should inform the institution Ethical Committee in case of any change of study procedure site and investigation or guide.
3. She/He should not deviate for the area of the work for which applied for Ethical clearance. She/He should inform the IEC immediately, in case of any adverse events pr Serious adverse reactions.
4. She/he should abide to the rules and regulations of the institution.
5. She/He should complete the work within the specific period and apply for if any Extension of time is required She should apply for permission again and do the work.
6. She/He should submit the summary of the work to the Ethical Committee on Completion of the work.
7. She/He should not claim any funds from the institution while doing the word or on completion.
8. She/He should understand that the members of IEC have the right to monitor the work with prior intimation.

Member Secretary **Chairman**

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The above PG student - thro' Head of the Department concerned.

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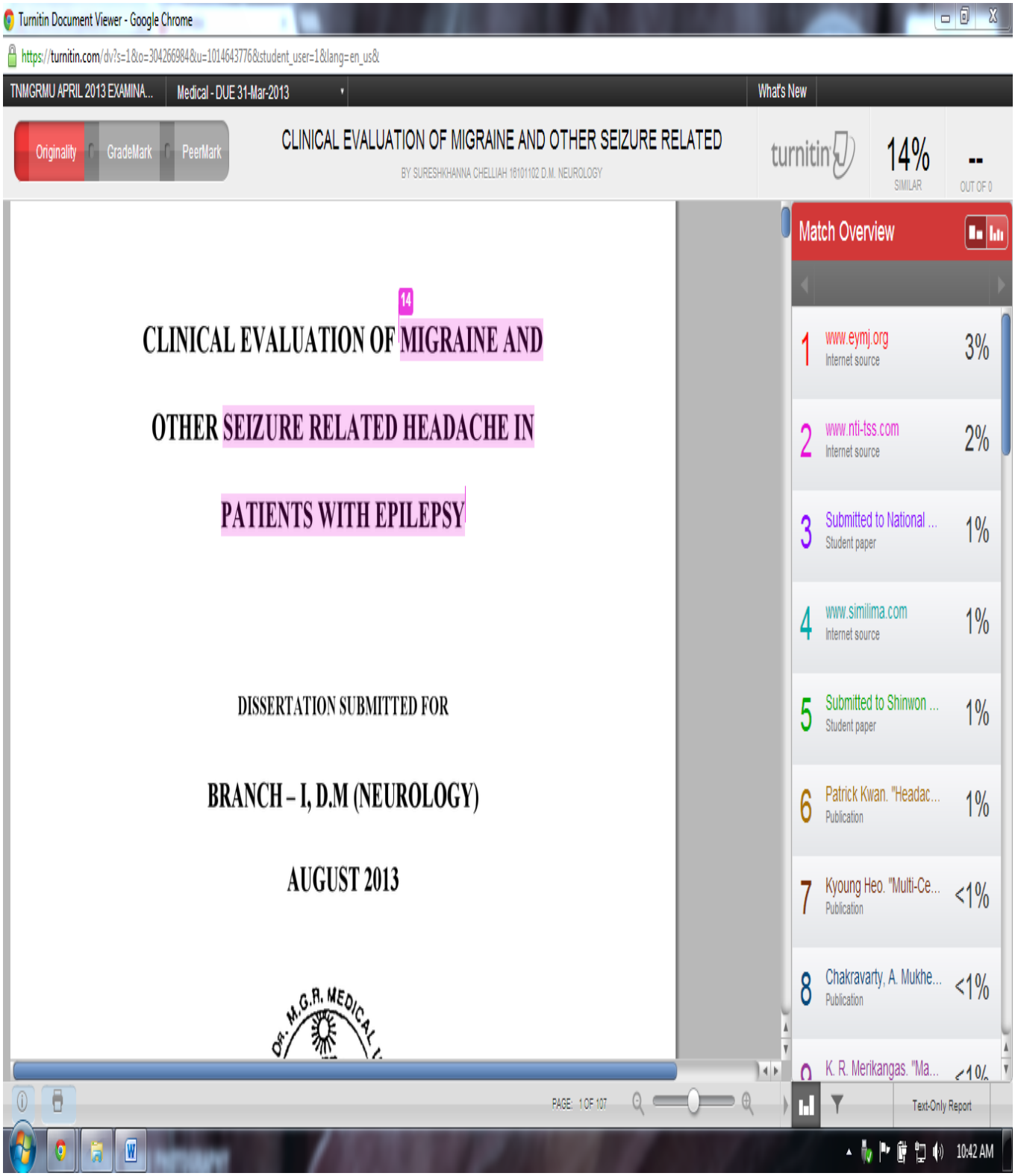
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